Medical Library

FEB 4 1946

SURGERY Gynecology and Obstetrics

With International Abstract of Surgery

VOLUME 82 February, 1946 NUMBER 2

This, too, is Preventive Medicine

For a large segment of our population this postwar adjustment period may present economic difficulties. In many such instances the first step toward "cutting down" will be to reduce food expenditures.

The advice to maintain nutrition, especially protein nutrition, may well be classed as sound preventive medicine.

Without sufficient protein intake—sufficient in quality as well as quantity—many phases of metabolic and functional life are bound to deteriorate.

An adequate amount of meat in the daily diet will go far in maintaining protein nutrition.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN MEAT INSTITUTE

MAIN OFFICE, CHICAGO . . . MEMBERS THROUGHOUT THE UNITED STATES

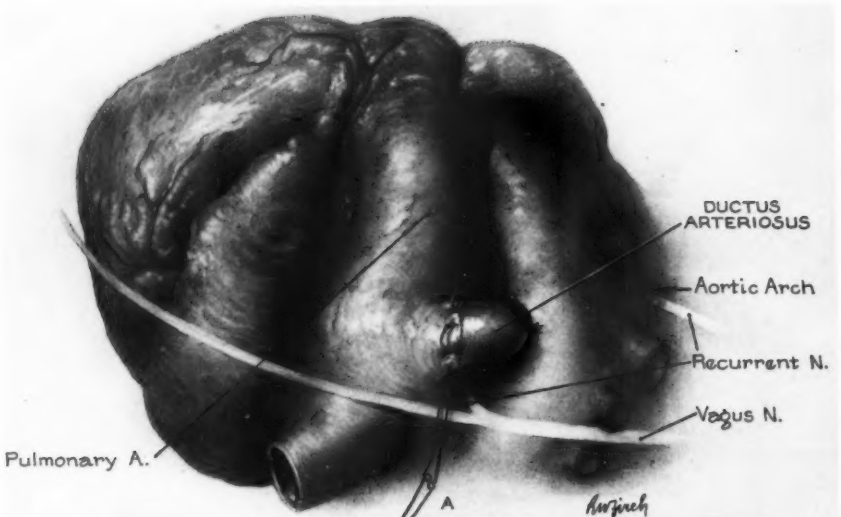


Fig. 1. A, Pursestring suture placed and tied on aortic side, placed but not tied on pulmonary side. B, Both pursestring sutures tied, mattress sutures placed. C, Mattress sutures tied, umbilical tape ligature placed. D, Umbilical tape tied.

Operative Closure of Patent Ductus Arteriosus.—Alfred Blalock.

SURGERY
GYNECOLOGY AND OBSTETRICS
An International Magazine, Published Monthly

VOLUME 82 FEBRUARY, 1946 NUMBER 2

OPERATIVE CLOSURE OF THE PATENT DUCTUS ARTERIOSUS

ALFRED BLALOCK, M.D., F.A.C.S., Baltimore, Maryland

ALTHOUGH a procedure for closure of the patent ductus arteriosus had been described by Munro in 1907 and although the operation had been attempted by Strieder (1), the first successful closure of an open ductus was performed by Gross (3) in 1938. The first method used by Gross was that of simple ligation of the ductus. It is well known that the lumen of a large artery which is closed by ligation "in continuity" may become patent again as the ligature cuts through the wall. Gross abandoned the method of simple ligation after having used it on 14 patients because there was evidence that the occlusion did not remain complete in several patients. More consistent closure of the ductus was obtained by Gross in 28 patients by the use of a second method in which the ductus was ligated and was also surrounded by cellophane. Some recurrences developed after this procedure and these led Gross (2) to develop a third method which consists of complete division and closure of the ductus. This procedure had been used on 14 patients at the time of the last report and the results were satisfactory.

It is because I question the necessity and safety of performing an operation in which the ductus is cut across and the ends closed that this brief communication is presented.

During a period of slightly less than 3 years my associates and I have operated upon 19 patients with patent ductus arteriosus, most of whom were referred by Dr. Helen Taussig. There have been no serious accidents during the operations and no postoperative deaths in the hospital. Two of the 6 patients who had a Streptococcus viridans infection died subsequent to discharge from the hospital. There was definite evidence in only 1 patient that the lumen of the ductus became re-established following the initial closure. Two ligatures of braided silk were used in closing the ductus of this patient. It was noted at the time of operation that the ductus was quite short and that the ligatures overlay each other. Following the development of evidence that the ductus had reopened, a second closure was performed. This patient had a Streptococcus viridans infection and she died 3½ months following the second operation.

We have used a number of different methods in our small series of cases. It is difficult to compare the effectiveness of the different methods because there has been evidence in only the 1 case referred to that the lumen of the ductus became re-established. In the earlier cases we used two ligatures of braided silk with or without an additional ligature of

From the Department of Surgery of The Johns Hopkins University and Hospital.

umbilical tape. In 2 patients the recent method of Gross (2) was modified to the extent that pursestring sutures of silk were placed at the extreme ends of the ductus. These were tied loosely and two straight clamps were placed on the ductus between the pursestring sutures. The ductus was divided between the clamps and the ends were closed with suture ligatures. Although no difficulty was encountered, it was felt that the division of the ductus probably exposed the patient to unnecessary danger of severe hemorrhage. We then adopted the method which has been employed in 7 patients and which is used at the present time. The entire length of the ductus is carefully dissected free of the adjacent structures. Pursestring sutures of medium silk on French needles are placed at the two extreme ends of the ductus. The adventitia is caught in the suture in several places. These sutures are tied loosely yet sufficiently tightly to abolish the flow of blood through the ductus. Two through-and-through mattress sutures of silk are placed and tied between the two pursestring sutures. A ligature of umbilical tape is then tied over the mattress sutures of silk. The method is shown diagrammatically in Figure 1.

There has been no evidence in the patients in whom this method has been used that the lumen of the ductus has become re-established. If subsequent experience corroborates this impression, it would seem that the method is preferable to that of division of the ductus because it subjects the patient to less danger of fatal hemorrhage. Even if division and closure of the ductus proves to be the method of choice, it would seem that the procedure can be made less dangerous by the preliminary placing of pursestring sutures at the extreme ends of the ductus.

REFERENCES

1. Graybiel, A., Strieder, J. W., and Boyer, N. H. Am. Heart J., 1938, 15: 621.
2. Gross, R. E. Surg. Gyn. Obst., 1944, 78: 36.
3. Gross, R. E., and Hubbard, J. P. J. Am. M. Ass., 1939, 112: 729.
4. Munro, J. C. Ann. Surg., 1907, 46: 335.

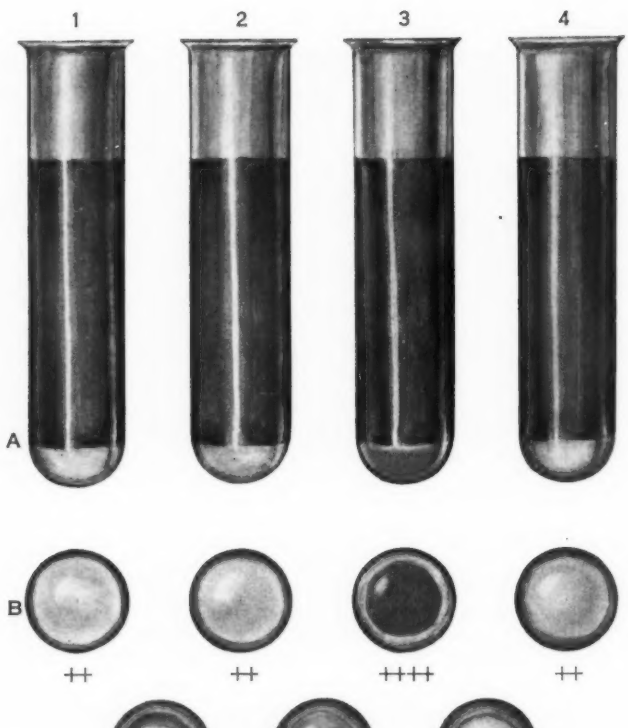


Fig. 1. Blood amylase activity as measured by cuprous oxide precipitation. A soluble starch was used. To measure decreased blood amylase activity it is advisable to use a more sensitive starch. Row A: Tube 1 is a normal control with a very small amount of a light brown cuprous oxide precipitate uniformly distributed on the bottom. This may sometimes come down as a very slender yellow ring.

Tube 2, Case 72835, group 1, is read as normal though a trifle more precipitate appears in it than in the control. The test was done during an attack of cholangitis. It was repeated twice and found normal on both occasions.

Tube 3, Case 73196, group 5 or Case 3 Table I, with blood amylase activity markedly increased. Acute hemorrhagic pancreatitis found at necropsy (see Fig. 2).

Tube 4, Case 73165, group 1 or Case 2 Table I, with blood amylase activity normal. Chronic pancreatitis found at operation. This patient recovered. Row B: The bottoms of tubes in Row A. Row C: Variations in the rings or buttons of precipitates obtained with soluble starch. When the more sensitive starch is used this is the type of precipitate one is apt to get with the normal control.

Blood Amylase Activity in Pancreatitis and Other Diseases.—David Polowe

Drawing by Alfred Feinberg

BLOOD AMYLASE ACTIVITY IN PANCREATITIS AND OTHER DISEASES

A Simple Diagnostic Aid

DAVID POLOWE, M.D., F.A.C.S., Paterson, New Jersey

IT is the purpose of this article to call attention to the evaluation of blood amylase activity in pancreatitis and other diseases and to a simple diagnostic aid, (16), which measures blood amylase activity in terms of cuprous oxide precipitation. The test is almost as simple as the determination of sugar in urine and it has now been used, with increasing success for over 4 years.

This study is based on 78 blood amylase activity determinations in 69 patients. In 62 patients the diagnoses were proved by acceptable criteria such as necropsy, operation, biopsy, x-ray, laboratory, or combinations of these. Though in 7 patients the diagnoses were unproved, the cases have been included in this series for the more conservative statistical evaluation of the incidence of proved pancreatic disease. In 63 patients the tests were run to rule in or to rule out acute pancreatitis, carcinoma of the pancreas, or to determine the blood amylase activity in biliary tract and other diseases. And the test was run in one case of pancreatic collection (pseudocyst) which was observed at the Newark City Hospital, the complete report of which is included in this series through the courtesy of Dr. R. O. Bauman.

CASE REPORTS

In this series of 69 cases there were 6 cases of acute pancreatitis proved at operation or at necropsy. The case of pancreatic collection was proved at operation. Because of its clinical importance a case of mesenteric and portal vein thrombosis, associated with a marked blood amylase activity, is also reported.

CASE 1. History No. 73165, M. L., female, white, aged 45 years, housewife, was admitted to the hospital May 15, 1943.

From the General Surgical Service, Barnert Hospital, Paterson, New Jersey, and the Thoracic Service, Bergen Pines Hospital, Ridgewood, New Jersey.

About 1 month prior to admission the patient suffered indigestion. She vomited after breakfast and had severe pain over the entire lower abdomen. The attack was accompanied by belching, a bitter taste, and pain which radiated to the back and to the shoulder blades. She gave a history of previous attacks of a similar nature.

On physical examination a marked enlargement of the abdomen was noted. A smooth, hard mass was felt in the pelvic region below the umbilicus. This mass was movable and not tender. There was marked distention in the epigastrium and tenderness over the gall-bladder region. However, the gall bladder could not be felt.

In the left upper abdomen there was a mass just below the left costal border which extended backward toward the kidney. There was tenderness in the left costovertebral angle. This mass felt more like the kidney than the spleen. It was thought that free fluid was in the peritoneal cavity. Moderate icterus was present.

Laboratory examinations of blood May 15, 1943 showed: icterus index, 35; hemoglobin, 12 grams per cent; red blood cells, 4,440,000; white blood cells, 21,200 with large, mononuclear leucocytes 4 per cent, lymphocytes 6 per cent, eosinophiles, none, band forms 9 per cent, polymorphonuclear leucocytes 81 per cent. Examination of the urine showed: specific gravity 1.013, a trace of albumin, no sugar, no acetone; on microscopic examination there were found a few white blood cells, an occasional red blood cell, no casts.

On May 18, 1943, 3 days after admission, a *blood amylase activity* test was performed and found to be normal (2 plus) (see Fig. 1, row A, tube 4).

On May 27, 1943, 12 days after admission, a supracervical hysterectomy was performed. At operation the gross findings were those of a large uterus with intramural fibromyomas, cholelithiasis, free fluid in the peritoneal cavity, and fat necrosis in the area of the pancreas.

On June 10, 1943, the patient was discharged, recovered. She was readmitted in August, 1943, and on August 23, 1943, a cholecystectomy was performed and the patient was subsequently discharged, recovered.

Pancreatitis as a cause for this patient's chief complaints was definitely considered prior to operation. The *blood amylase activity* test was found to be normal. It is a known

fact that blood amylase activity rises sharply at the onset of an attack of acute pancreatitis and may subside just as sharply within 72 hours of the onset. For that reason one should not sacrifice the judgment gained by years of clinical experience for a noncorroborative diagnostic laboratory aid. Briefly, a normal blood amylase activity report does not rule out the presence of acute pancreatitis, whereas a moderately or markedly increased blood amylase activity rules strongly in favor of acute pancreatitis.

Attention is invited to the fact that the patient was observed for 12 days prior to the first operation when the pelvic pathological lesion was removed. The initial symptoms had subsided, the patient was in good condition for operation, all thoughts of acute pancreatitis had vanished in the light of the normal blood amylase activity so that the presence of fat necrosis in the area of the pancreas came as a mild surprise.

CASE 2. History No. 72495, D. V., female, white, aged 53 years, was admitted to the hospital March 20, 1943, with a chief complaint of pain in the epigastrium of 6 months' duration. The pain was more severe after she ate heavy food and was occasionally associated with vomiting. In the past 3 months the epigastric pain was much more severe and came more often. She had lost 10 pounds (4.5 kgm.) of weight in the past 3 months. The epigastric pain had been very severe for the past 10 days.

On physical examination there was found a definite tenderness in the epigastrium and right upper quadrant of the abdomen. A mass was palpable in the gall-bladder region, and it extended two fingers below the costal margin. The temperature was 100 degrees (37.2° C.); pulse 68, regular; blood pressure 130 millimeters of mercury systolic, 80 millimeters of mercury diastolic.

Laboratory examination of urine showed specific gravity 1.020; albumin, a trace; no sugar; acetone, a trace. Examination of the blood showed hemoglobin 13 grams per cent; red blood cells 3,690,000; white blood cells 7,900 with large mononuclear leucocytes 2 per cent, lymphocytes 14 per cent, eosinophiles 1 per cent, polymorphonuclear leucocytes 83 per cent.

Clinical impression: acute cholecystitis.

On March 23, 1943, 3 days after admission, operation was performed. A hemorrhagic pancreatitis with fat necrosis, cholecystitis, and cholelithiasis were found. Cholecystostomy, removal of gall stones, and drainage were done.

The pathologic report (by Lt. J. Churg): (1) Portion of gall-bladder wall showed edema and chronic inflammation; (2) cholelithiasis; (3) portion of fat tissue showed small areas of necrosis.

The *blood amylase activity* test was performed 3 days *after* the operation and was moderately (3 plus) increased. The patient was not relieved by the operation. She became depressed, continued to vomit, and finally expired on May 1, 1943, 39 days after the operation.

Since only one blood amylase activity test was performed we are left in the dark as to the changes that took place in the pancreas from a secretory point of view. There was no necropsy so we do not know the exact cause of death. We were left with the impression that a moderate blood amylase activity increase may be associated with a serious prognosis in acute pancreatitis. This case also emphasized the fact that blood amylase activity tests should be run every day or every other day since it is known that blood amylase activity usually parallels the course and the clinical symptoms of pancreatitis (10).

CASE 3. History No. 73196, J. J., male, aged 69 years, was admitted to the hospital May 17, 1943, and died May 19, 1943.

His chief complaint was: severe abdominal pain and vomiting. The onset occurred on May 13, 1943, with pain in the precordium which extended down the left arm. This recurred the following day, May 14, 1943. On May 17, 1943, the patient was seized with severe pain in the upper abdomen followed by continuous vomiting. The patient then developed severe shock associated with a subnormal temperature and a cold, clammy skin.

The patient had had an attack of severe abdominal pain followed by nausea and vomiting in October, 1941. At that time there was some tenderness over the abdomen but no rigidity.

Physical examination revealed a soft, distended abdomen, with no areas of rigidity, but tenderness was present on pressure and rebound.

Laboratory examinations revealed white blood cells 21,500 with a marked shift to the left. *The blood amylase activity* was markedly increased (4 plus) (see Fig. 1, row A, tube No. 3.)

The patient went rapidly downhill with a rising temperature. He died 48 hours after admission.

The pathologic diagnosis (necropsy by Lt. J. Churg) was as follows: acute hemorrhagic pancreatitis; widespread peritoneal and retroperitoneal fat necrosis; periesophageal fat necrosis; hemorrhagic effusion in the peritoneum (800 c.c.) and in both pleural spaces (200 c. c.); chronic cholecystitis and cholelithiasis; pulmonary emphysema; atelectasis of both lower lobes; pulmonary edema and congestion; arteriosclerosis of the kidneys.

Acute hemorrhagic pancreatitis was the cause of death but coronary thrombosis was the foremost clinical diagnosis in the minds

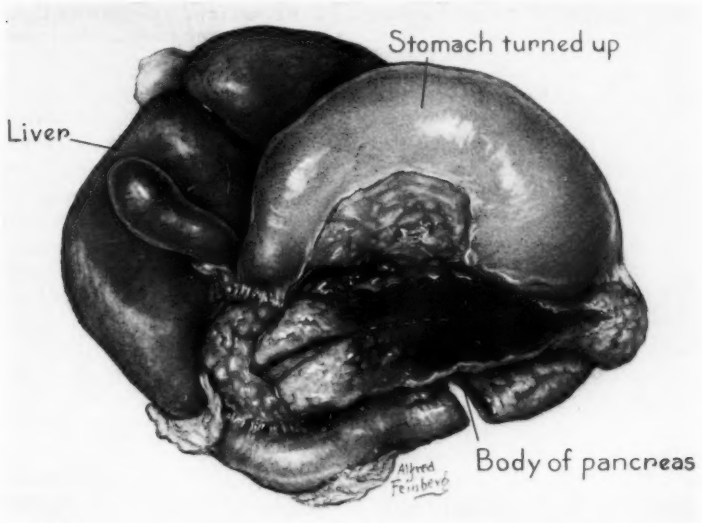


Fig. 2. Gross specimen of Case 73196, group 5, or Case 3, Table I: The under surface of the liver, the gall bladder and the stomach are turned up. The pancreas has been cut transversely and opened like a book. The acute hemorrhagic process can be seen in the body and the tail of the pancreas. There were numerous plaques of fat necrosis in the head and tail of the pancreas as well as in the peritoneal and retroperitoneal structures.

of the attending physicians for 3 days prior to admission of the patient to the hospital when the clinical state of the patient was that of epigastric pain and vomiting. A diagnosis of acute hemorrhagic pancreatitis was then made and confirmed first by the *marked increase (4 plus) in blood amylase activity*, and then by necropsy (Fig. 2).

CASE 4. History No. 76645, S. E., male, white, aged 44 years, was admitted to the hospital February 28, 1944, with a chief complaint of severe epigastric pain, followed by nausea and vomiting. The present illness began 2 days prior to admission. In September, 1943, the patient had suffered a severe attack of epigastric pain associated with severe vomiting and nausea. There was no jaundice and the pain radiated to the right shoulder. The pain started suddenly and stopped suddenly. The patient was well for 2 weeks and then had a repetition of the symptoms named. In October, 1943, an x-ray series revealed the presence of stones in the gall bladder. Shortly after this the patient suffered another attack of severe epigastric pain. He was placed on a strict diet and was free from pain until 2 days prior to admission on February 28, 1944.

On physical examination, the patient appeared to be acutely ill. There was no clinical icterus. The abdomen was distended, and there was an associated marked rigidity and exquisite tenderness in the right upper quadrant of the abdomen over the gall-bladder region. There was no tenderness in the costovertebral angles. The temperature was 99 degrees (37.2° C.), the pulse 94, respirations 18.

Laboratory examination of the urine revealed: reaction, acid; specific gravity, 1.030; albumin, a trace; sugar, 3 plus; acetone, negative. On microscopic examination a few white blood cells were found, but no red blood cells, no casts or bacteria were present. Blood count showed white blood cells, 18,500; hemoglobin 17.0 grams per cent; red blood cells 5,590,000.

Clinical impression: acute cholecystitis with cholelithiasis.

Cholecystectomy and choledochotomy were performed on the day of admission, February 28, 1944. A large amount of bloody fluid was present in the peritoneal cavity. There was hemorrhage into the pancreas. Fat necrosis of the pancreas was present, and a large number of stones were found in the gall bladder. The common duct was distended but no stones were found in it.

March 1, 1944, 2 days *after* the operation, a *blood amylase activity* test was performed and reported markedly increased (4 plus).

Pathologic diagnosis (by Dr. A. J. Gitlitz): acute cholecystitis with prominent acute pericholecystitis; omental fat showing areas of fat necrosis and nonspecific acute inflammation; chronic cholecystitis

and cholelithiasis; cholesterosis of the gall bladder.

The patient was discharged, recovered, on March 21, 1944, with a final diagnosis of acute and chronic cholecystitis, cholelithiasis, cholesterosis of the gall bladder, and acute hemorrhagic pancreatitis.

Acute hemorrhagic pancreatitis was not suspected before operation in this case. The blood amylase activity test was run off 2 days after operation to determine what it would show. It was markedly increased (4 plus). We can only speculate as to how the case might have been handled had the test been run before operation. It serves to emphasize the fact that in every case of acute upper abdominal distress acute pancreatitis must be kept in mind or else the diagnosis is apt to be missed.

CASE 5. History No. 79855, H. R., white, male, aged 47 years, was admitted to the hospital November 17, 1944, and died November 20, 1944. He had been brought home from work November 16, 1944, with a chief complaint of severe epigastric pain and vomiting. He was constipated but passed one watery stool on the day of admission to the hospital. He had had a similar attack 3 years before, when he was also hospitalized (History No. 66586), consultations held, a diagnosis of acute appendicitis made. No operation was performed, however, because of the atypical symptoms which subsided in a few days, he having been admitted November 4, 1941 and discharged November 10, 1941.

Physical examination at present admission revealed a patient in severe shock and pale. The findings in general were noncontributory except those of the abdomen which was rigid and markedly distended.

A flat x-ray plate of the abdomen revealed ". . . . a gaseous distention of the large and some of the loops of the small intestine. The large intestine is visualized down to the sigmoid, and it is not sufficiently dilated to make a diagnosis of obstruction."

The blood count on November 18, 1944, revealed white blood cells, 21,950, stab forms 11 per cent, segmented polymorphonuclear leucocytes 50 per cent, lymphocytes 38 per cent, monocytes 1 per cent. The blood sugar was 140 milligrams per cent. The *blood amylase activity* was moderately increased (3 plus).

The clinical diagnosis was intestinal obstruction. Ileostomy was performed November 19, 1944. This was done as rapidly as possible and, though the broth-like fluid in the peritoneal cavity was noted, its true significance escaped attention until necropsy the following day.

The pathologic diagnosis (necropsy by Dr. A. J. Gitlitz) was as follows: acute hemorrhagic pancreatitis with retroperitoneal and intramesenteric hemorrhage and scattered omental and mesenteric fat necrosis, and splenic vein thrombosis; chronic cholecystitis and cholelithiasis.

This was a fulminating case of acute hemorrhagic pancreatitis which was diagnosed and treated as a case of intestinal obstruction. The blood amylase activity was determined *before* operation. It was moderately increased (3 plus). While a normal blood amylase activity does not rule out the presence of acute hemorrhagic pancreatitis, a moderately or markedly increased blood amylase activity finding almost always signifies the presence of pancreatic disease.

CASE 6. History No. 82077, L. S., white, female, aged 56 years, was admitted to the hospital May 21, 1945, with a history of sudden pain in the gall-bladder region 10 days prior to admission. The pain was intermittent for the following 8 days and continuous for the next 2 days. The pain radiated to the back and to the right shoulder. Nausea was present throughout this period and the patient vomited on two occasions. There was no change in color of the feces, but clinical icterus developed and the urine was dark brown. The patient was a quadrigravida, tripara with onset of menopause 10 years previously. She had lost 15 pounds (7.6 kgm.) in the past year during which time she suffered from a nocturia and urinary frequency. The patient had had a cholecystectomy and appendectomy performed 16 years previously.

The patient's temperature was 100 degrees F. (37.2° C.), pulse 80, regular, respirations 20, blood pressure systolic 170 millimeters of mercury, diastolic 80 millimeters of mercury. Icterus of the skin and sclera was present. Her tongue was dry and coated. There was definite tenderness in the epigastrium to the left and right of the midline. Opinion was divided as to which side the tenderness was most pronounced.

Laboratory examination of the urine revealed bile, positive; urobilinogen, positive up to 1:40. Blood chemistry, May 23, 1945 revealed: nonprotein nitrogen 40 milligrams per cent; icterus index 20; sedimentation rate 20 millimeters in 1 hour by the Wintrobe method; stool for occult blood, negative; *blood amylase activity* moderately increased (3 plus). May 24, 1945, white blood cells 4,650 with stab forms 2 per cent, polymorphonuclear leucocytes 51 per cent, eosinophiles 3 per cent, lymphocytes 43 per cent, monocytes 2 per cent; hemoglobin was 13 grams per cent; red blood cells 3,920,000.

On May 28, 1945 *blood amylase activity* was barely visibly increased (recorded as 2½ plus); icterus index, 10. X-ray examination of the gall bladder, stomach, and duodenum was reported as, "Gall bladder not visualized. Stomach and duodenum: No pathology."

On May 29, 1945, blood cholesterol was 155 milligrams per cent.

On May 31, 1945, cephalin flocculation test was negative; Kahn and Mazzini tests, negative.

Operation was performed on May 31, 1945. There were many postoperative adhesions at the site of the cholecystectomy. The pancreas was indurated, nodular, and plaques of fat necrosis were clearly visible in the head, body, and tail of the pancreas. The common duct was slightly dilated. This was aspirated and a clear, golden bile was obtained. The adhesions were released, the common bile duct was probed thoroughly for gall stones but none was found. Choledochotomy was then performed.

The presence of icterus made it necessary for us to rule in or to rule out common duct stone or pancreatitis or both. Carcinoma of the head of the pancreas was considered but this diagnosis was discarded because of the sudden onset of severe epigastric pain. We felt reasonably certain that we were dealing with a case of acute pancreatitis because of the increased blood amylase activity, but we could not rule out the presence of a common duct stone without an exploratory operation.

The patient improved markedly under conservative therapy, and the blood amylase activity and clinical icterus decreased. The patient was given the option of going home, to return for operation if she suffered another attack, or to be operated upon while she was in good condition in the hospital. She chose operation at once because the pain had been so severe that she did not wish to run the risk of experiencing it again. She had a smooth postoperative course and was discharged, recovered, June 28, 1945.

CASE 7. History No. 76131, H. H., male, aged 47 years, was admitted to the hospital January 16, 1944; died January 17, 1944.

There was a history of indefinite gastric distress for 3 weeks. During this period the patient developed a cough with fever, diarrhea, and weakness suggesting a diagnosis of influenza. On Sunday, January 16, 1944, the patient awakened during the night with excruciating pain in the abdomen. This pain was not relieved by morphine administered hypodermically.

One and one-half years prior to admission to the hospital, the patient sustained an injury to his toe which fractured it. Following this he developed a thrombophlebitis in the opposite extremity and metastatic infarcts to the lungs ensued.

On the present admission to the hospital the patient was ashen gray, pulseless, cold, clammy, and in complete shock. He was treated for shock and felt a little better. A Levine tube was passed and revealed what appeared to be blood. The patient became progressively worse under treatment and just before death on January 17, 1944, he passed blood per rectum. There was no previous history of a gastric disorder and his bowels were fairly regular until the present illness.

The temperature ranged between 101 and 102 degrees F. (38.3° and 38.9° C.); pulse, 144; respiration rate ranged between 18 and 40 per minute. The chest disclosed no abnormalities. The heart sounds were very faint. The abdomen was slightly distended, not spastic, and not rigid. There was slight tenderness in the epigastrium. The liver edge was palpated at the costal margin. The spleen and kidneys were not palpable. The skin was cold and clammy. The glands were not enlarged and the neurologic examination exhibited no abnormalities.

Laboratory examination revealed white blood cells, 23,100; stab forms 22 per cent, polymorphonuclear leucocytes 58 per cent, lymphocytes 20 per cent; red blood cells 4,350,000, hemoglobin 14.5 milligrams per cent. Urine examination revealed: sugar and acetone, 2 plus. Blood hematocrit was 55 per cent; blood sugar, 335 milligrams per cent. The *blood amylase activity* was moderately but definitely increased (3½ plus).

Clinical diagnosis: acute hemorrhagic pancreatitis.

Pathologic diagnosis (necropsy by Lt. J. Churg) was; thrombosis of superior mesenteric and portal veins; hemorrhagic infarction of almost the entire small intestine; hemorrhagic peritoneal effusion (1500 c. c.); old pulmonary infarcts; acute and subacute pleuritis; myocardial fibrosis, mild; fatty changes of the liver; pulmonary emphysema; fibrous pleural adhesions.

This case is of interest because it illustrates how carefully one must evaluate the past history and because it brings out the importance of securing necropsies. The possibility of mesenteric thrombosis was entertained but discarded in favor of a clinical diagnosis of acute hemorrhagic pancreatitis because of the moderate, but definite, increase in blood amylase activity. We did not know then, as we know now, that mesenteric and portal vein thrombosis may be associated with an increased blood amylase activity. And were it not for the necropsy, the finding of an increased blood amylase activity would have led us to record this as a case of acute hemorrhagic pancreatitis.

CASE 8. No. 364105, E. T., female, white, aged 39 years, was admitted to the hospital April 21, 1942, discharged June 18, 1942.

The patient's chief complaint on admission to the hospital was vomiting of 1 week's duration. The vomitus included solids and fluids immediately after ingestion. All other symptoms are lacking. All antecedent history is noncontributory.

TABLE I.—SUMMARY OF 6 CASES OF PANCREATITIS PROVED AT OPERATION OR AT NECROPSY

Case No.	History No.	Diagnosis and remarks	Blood amylase activity
1	72495	Chronic pancreatitis, cholecystitis, cholelithiasis. Operation 3-23-43 cholecystotomy. Died 5-1-43	3 plus. Test done 3 days postoperative
2	73165	Chronic pancreatitis, cholecystitis, cholelithiasis, fibromyoma uteri. First operation 5-27-43, hysterectomy. Discharged, recovered, 6-10-43. Second operation 8-23-43, cholecystectomy. Discharged, recovered.	2 plus (normal). Test done 6 days prior to first operation
3	73196	Acute hemorrhagic pancreatitis, chronic cholecystitis, cholelithiasis. Admitted 5-17-43. Died 5-19-43. Necropsy	4 plus. Test done the day of admission
4	76645	Acute hemorrhagic pancreatitis, chronic cholecystitis, cholelithiasis. Operation 2-28-44, cholecystectomy and choledochotomy. Discharged 3-21-44, recovered	4 plus. Test done 2 days postoperative
5	79855	Acute hemorrhagic pancreatitis, chronic cholecystitis, cholelithiasis. Admitted 11-17-44. Operation 11-19-44, ileostomy. Died 11-20-44. Necropsy.	3 plus. Test done the day before operation
6	82077	Acute pancreatitis (pancreas indurated, nodular, associated with fat necrosis). Cholecystectomy performed 16 yr. prior to present admission. Admitted 5-21-45. Operation 5-31-45, choledochotomy. Discharged 6-28-45, recovered	3 plus. Test done 2 days after admission. 2½ plus 5 days later, associated with clinical improvement, 3 days prior to operation

On admission the patient was in no distress. She was well developed, well nourished, and exhibited no rashes or icterus. The positive findings were as follows: blood pressure 130 millimeters mercury systolic, 90 millimeters mercury diastolic. In the left upper quadrant of the abdomen there was a mass about the size of a grapefruit which protruded only slightly above the abdominal contour. This mass extended into the epigastrium where it was tender. The possibility of two masses was considered.

Provisional diagnosis: malignant growth of the stomach; splenomegaly of unknown etiology.

Retrograde pyelography disclosed no pathological process; cystoscopy disclosed none. Peritoneoscopy revealed a mass in lesser omental cavity, perhaps a cyst of the pancreas; the stomach displaced anteriorly. X-ray (barium enema) examination revealed evidence of pressure at distal third of transverse colon and splenic flexure probably due to extrinsic pressure; chest examination revealed left diaphragm flat and slightly elevated. Thoracic and lumbar vertebrae showed no evidence of the presence of pathology.

Laboratory examination of the urine revealed albumin, 2 plus; concentration good. Examination of feces for undigested fats gave normal findings. Blood chemistry examination revealed: normal values for sugar, urea, nonprotein nitrogen, and creatinin. White blood count showed 9,150; polymorphonuclear leucocytes 64 per cent. Red blood cells numbered 3,000,000 to 4,000,000; hemoglobin range was 56 to 60 per cent.

The size of the mass fluctuated slightly, and its tenderness was intermittent. On the fourth day of admission the patient awoke with severe substernal pain which did not radiate. This attack was accompanied by profuse diaphoresis. Dyspnea was experienced but no cyanosis was visible. There were no chest signs.

Clinical impression: (1) possible small pulmonary embolus; (2) possible coronary episode.

The abdomen continued to be painful and the patient was brought to surgery. A left rectus incision revealed a fluctuant mass above and behind the stomach. The foramen of Winslow was closed. A nick was made in the gastrohepatic mesentery, and the mass was drained of about 2000 cubic centimeters of brown, bile-stained or coffee-colored fluid with little odor. This sac was packed with plain gauze. The sac was marsupialized and the gauze was left hanging outside. The abdomen was closed in layers after a piece of the sac wall was excised for biopsy.

The postoperative course was uneventful. The cavity continued to drain small amounts of coffee-colored fluid. The drain was ultimately removed and the patient was discharged, 5 weeks after admission.

A biopsy specimen of the cyst wall revealed fibroblastic tissue. Organisms were not found. The *blood amylase activity*, done several days after operation, by the cuprous oxide precipitation method (16), was found to be *markedly increased* (4 plus).

A letter from Dr. Richard O. Bauman, dated June 18, 1942, states: "Enclosed is a summary of the case you were interested in. She is now discharged even though she has considerable drainage from the marsupialized sac or cyst.

"It was the opinion of some of the men on the staff that this lesion came under the group classified as pseudocysts of the pancreas. Biopsy of the cyst wall and other evidence, such as a closed foramen of Winslow and the presence of old inflammatory fibrosis seem to substantiate this, but then again, we could not be sure. A follow up is in order."

The patient could not be followed up further.

The increased blood amylase activity found in this case helped the staff lean toward a diagnosis of pseudocyst of the pancreas. Pinkham, in a review and analysis of 10 cases of pancreatic collections (pseudocysts), states

that, "Persistent elevation of the serum amylase following the signs and symptoms of pancreatitis or pancreatic necrosis is significant, indicating the probable development of a pancreatic collection."

Thus we are once again reminded that single blood amylase determinations, while very valuable in the acute case, are not as valuable as repeated determinations where the clinical diagnosis is in doubt and the condition of the patient permits study over a period of days prior to operation.

ANALYSIS OF CASES

Group 1. Of the 69 patients tested 37 (53.6 per cent) were found to have a normal blood amylase activity. As we gained experience with the interpretation of blood amylase activity we discovered that a normal blood amylase activity is a true source of comfort. In only 1 instance (Case No. 73165, which is reported here in detail) was a proved pancreatitis found associated with a normal blood amylase activity, and this patient recovered.

A white female, aged 60 years, Case No. 75446, was admitted to the hospital with a chief complaint of severe epigastric pain and vomiting. This was associated with an intense icterus. She had had a cholecystectomy 10 years before. A gastrointestinal x-ray series revealed the presence of a tiny herniation of the stomach through the diaphragm, a duodenal diverticulum, a shadow as of a stone in the region of the right kidney or gall-bladder bed. Consultations were held. A clinical diagnosis of common duct stone was made and it was desired to rule out an associated acute pancreatitis. The *blood amylase activity* was normal. A stone in the common bile duct was found at operation. The pancreas was not inflamed. A choledochotomy was performed, the stone was removed, and the patient made an uneventful recovery.

Case No. 79776 illustrates the use of blood amylase activity determinations in the location of intestinal obstruction. In 1933 it was reported (15) that increased blood amylase activity may be found in high intestinal obstruction and in 1940 Johnson and Bockus reported an elevated serum lipase in intestinal obstruction. It is conceivable that pancreatic enzymes may be reabsorbed into the general circulation from severely distended small intestines before viability of their walls is lost.

In Case 79776, the diagnosis of intestinal obstruction was quite certain and the *normal blood amylase activity* not only served to rule out acute pancreatitis but made it seem likely that the obstruction was low. At operation the ileum was found twisted on itself and so adherent to the posterior parietal wall of the peritoneum in the right vertebral gutter that it could not be released without fear of tearing it. An ileostomy was performed. The patient died 12 hours later. At necropsy, 5 days after the onset of the illness, 1 foot of ileum was found gangrenous about 1 foot from the cecal end. This gangrenous loop of ileum was found firmly caught under a free edge of the root of the mesentery and explained the inability of the operator to free this 12 hours earlier.

Group 1 includes 3 patients with serious kidney pathology (cases Nos. 77219, 80353, and 82145), with carcinoma of the right kidney, left pyelitis cystica, and uremia, respectively. Since urine excreted by normally functioning kidneys has an amylase activity of 2 to 6 times that of blood, many attempts have been made to correlate kidney function with blood amylase activity or urinary amylase activity. It is reasonable to expect a normal blood amylase activity in the first 2 cases mentioned because only one kidney was involved in each of these patients. In the third case in which the patient died of uremia one is at a loss to account for the normal blood amylase activity for with markedly diminished kidney function one does expect an increased blood amylase activity. However, the problem is not as simple as all that, for it is conceivable that associated liver damage may be the responsible factor. Considerable study is required to correlate kidney function with blood and urinary amylase activity. Dozzi has concluded that there is no quantitative relationship between blood and urinary amylase.

Eleven patients with biliary tract disease appear in group 1. Since in our experience acute pancreatitis was found associated with biliary tract disease in all (100 per cent) of the 6 proved cases of acute pancreatitis, a normal blood amylase activity in biliary tract disease has come to be regarded by us as safely excluding an associated acute pancreatitis or that a pre-existent acute pancreatitis is subsiding.

Group 2. In group 2 are 7 cases with decreased (1 plus) or absent (zero) blood amyl-

ase activity (10.1 per cent of the 69 patients observed). In this group the decrease was in no instance associated with acute pancreatitis.

The liver is considered by some observers, among them Dozzi, to play some part, at least, in the formation of amylase. For that reason a decreased or absent blood amylase activity has been interpreted as evidence of impaired liver function. Lewison has reported a depressed serum amylase in liver disease. Bartlett studied blood amylase activity in thyroid disease and concluded that a decreased blood amylase activity indicates impaired liver function in that condition.

A decreased or absent blood amylase activity may be found in any chronic, wasting disease such as tuberculosis (4 cases) or carcinoma (1 case). In tuberculosis amyloidosis of the liver is a common finding. In carcinoma of the stomach metastatic nodules may replace most of the normal liver tissue.

There were 2 cases of biliary tract disease in group 2—decreased (1 plus) or absent (0) blood amylase.

The first, H. W., a white female, aged 68 years, was admitted with a chief complaint of severe right upper abdominal pain. This pain was associated with an intense icterus. X-ray examination disclosed a nonfunctioning gall bladder. The laboratory reported a blood picture of severe pernicious anemia with a red blood cell count below two million. The *blood amylase activity* was decreased (1 plus). The patient improved remarkably under crude liver extract therapy and was discharged, improved. A year later she suffered another attack of gall-bladder colic and submitted to operation; chronic cholecystitis and cholelithiasis were found, cholecystectomy performed and the patient is alive and well today though she has to continue with liver extract therapy.

Since in Group 1 there were 2 cases of pernicious anemia (Nos. 72400 and 81248) and 11 cases of biliary tract disease, one cannot be sure that pernicious anemia *per se* is responsible for the decreased blood amylase activity in the first case in group 2 (H.W.) nor that the biliary disease is responsible for the decreased blood amylase activity in both Case 1, H. W., and No. 74702 in group 2.

Suffice it to say that in the present state of our knowledge of decreased blood amylase activity one may safely regard such decrease as ruling out serious pancreatic disease. And that while a decreased blood amylase activity may point toward decreased liver function one should use other and better known liver function tests when the function of the liver is under investigation.

Group 3. In group 3, there were 9 cases with slightly increased (2½ plus) blood amylase activity (13.1 per cent of the 69 patients observed). In none of these were we able to prove that acute pancreatitis was present. Several impressions were gained from a study of these cases of slightly increased blood amylase activity: (a) single determinations of blood amylase activity are not as valuable as repeated determinations; (b) a mild pancreatic edema accompanies such clinical entities as biliary tract disease, blockage of the lymphatic system, and in pneumonitis secondary to cardiovascular disease; (c) that variations in blood amylase activity may be expected in thyroid disease.

Whenever a single determination of blood amylase activity is reported as slightly increased the test should be repeated every day or every other day. In a pancreatitis which is subsiding, remaining stationary, or is getting worse, there is usually a concomitant decreasing, stationary, or increasing blood amylase activity. This statement is based not only upon my own experience but also upon the experience of others, notably, McCorkle, Goldman and Cornell, who made 909 blood amylase activity determinations in 48 cases using the method of Somogyi. They state: "Serum amylase usually parallels the course of the disease and clinical symptoms . . . . though the latter may clear before the blood amylase is normal."

When the biliary tract is involved as in Cases 73289, 73303, and 80219, we are no longer surprised to find a slight increase in blood amylase activity since in all 6 of our proved cases of acute pancreatitis there was associated biliary tract disease. This also brings up the question as to whether biliary tract disease causes acute pancreatitis or whether chronic pancreatitis causes biliary tract disease. Weiner analyzed 4000 necropsies and found that, "The incidence of gall-bladder disease is significantly increased in pancreatitis but the incidence of pancreatitis in

gall-bladder disease is only slightly, if at all, higher than in the general autopsy series." Colp, Gerber, and Doubillet state that cholecystitis may be due to pancreatic reflux, and Wolfer has found that pancreatic juice may be the etiologic factor in the production of cholecystitis in the dog. Weiner was able to show that a common channel may exist between the common bile duct and the pancreatic duct without the development of acute hemorrhagic pancreatitis. Our pathologist, Dr. A. J. Gitlitz, states that reflux bile *per se* is not always a cause for pancreatitis. In the 2 of our 6 proved cases of acute pancreatitis which came to necropsy no bile was found in the pancreatic ducts, and Dr. Gitlitz states that he has examined postmortem at least 3 other cases of acute hemorrhagic pancreatitis in which no bile was found in the pancreatic ducts.

Dragstedt, Haymond, and Ellis have shown that in 60 per cent of the cases of acute hemorrhagic pancreatitis, there was an antecedent biliary tract disease. In 10 per cent of these a common channel was produced by the impaction of gall stones in the ampulla of Vater. In the majority of the remainder, a common channel was produced by spasm of the sphincter of Oddi or edema of the papilla. They state that in cases in which bile is not the etiologic factor then concentration of the alkali of pancreatic juice is the destructive factor just as concentration of acid in the gastrium may be the destructive factor in that location.

Thus a study of the literature makes it apparent that both the "common channel theory" of bile reflux and the obstructive theory with its concomitant concentration of the alkaline pancreatic juices within the pancreas are both tenable etiologic factors in the production of acute pancreatitis. And the pancreatic reflux theory is a plausible explanation for the high incidence of cholecystitis in pancreatic disease. When these theories are understood and reflected upon, it becomes easier for the clinician to interpret blood amylase activity in biliary tract disease, and the need for repeated blood amylase activity determinations in the borderline case becomes more apparent.

Blockage of the lymphatic system may cause an increase in blood amylase activity. In case No. 73653 in which there was a mesenteric cyst about 15 centimeters in diameter and in case No. 74118 in which there were retroperitoneal metastases from an embryonal cell carcinoma of the testes, a slightly increased blood amylase activity was found. The mechanism of this increase in blood amylase activity cannot be explained entirely. Shafiroff, Price and Polowe, cited by Polowe (14), ligated the thoracic duct and the common bile duct in 1 dog (dog 4). There was an immediate rise in blood amylase activity, and this rise was sustained for 48 hours when the dog died. One can only speculate as to whether the ligation of either duct alone would produce this result or whether it takes both conditions combined to do so. The impression at present is that, since the lymphatic system is in close communication with the venous system throughout the body, lymph with its accompanying enzymes backs up into the general venous circulation when the lymphatics are blocked.

Popper and Necheles cannulated the thoracic ducts in 3 dogs and occluded the portal vein in a 4th dog. They damaged the pancreas in these dogs by the injection of 0.1 to 4 cubic centimeters of bile into the pancreatic duct. They then determined the amylase and lipase activity in the peripheral blood, the portal blood, and the lymph. They concluded that the main pathway of pancreatic enzymes into the peripheral blood following injury to the pancreas is by way of the portal vein and to a lesser extent by inflow of enzymes by the lymph of the thoracic duct. Their findings are corroborated clinically by cases Nos. 73653 and 74118 and the *slight* increased blood amylase activity found with blockage of the lymphatic system and case No. 76131, with superior mesenteric vein and portal vein thrombosis (reported in detail in the fore part of this paper) and its accompanying *marked* increase in blood amylase activity.

From the foregoing one can readily understand how necessary it is to study the history and clinical findings in each case in order to evaluate properly the blood amylase activity found.

There were 2 cases of pneumonitis secondary to serious cardiovascular disease in group 3. These were Case D. M. and No. 80232.

Case D.M., a well known surgeon in our community, became ill suddenly in 1941. The principal manifestations were pain in the right chest, severe epigastric pain, nausea, and vomiting. The patient had had some form of intestinal surgery several years before, and this was followed by an incisional hernia. Consultations were held. Roentgenograms of the chest disclosed a right lower lobe pneumonitis. The attending physicians thought that he might be suffering from either high intestinal obstruction or acute pancreatitis. A *blood amylase activity* test was ordered. Especial care was used in this instance because it was our first serious case in which the cuprous oxide precipitation method was being tried. It was found to be slightly increased (2½ plus). It was my opinion, given at that time, that this finding was not compatible with an acute pancreatitis but could be compatible with either a pneumonitis or a high intestinal obstruction. The patient's symptoms cleared, and subsequently it was discovered that the patient had a thoracic aneurysm. The patient died suddenly 2 years later when the aneurysm ruptured.

Since acute pancreatitis may simulate coronary thrombosis case No. 80232 merits attention.

The patient, a white male, aged 52 years, was admitted December 22, 1944, and expired January 6, 1945. There was no necropsy. The important manifestations were severe precordial and abdominal pain, dyspnea, pallor, abdominal distention. The final diagnosis was coronary thrombosis with myocardial infarction, but a progress note made the day before the patient died is of interest: "January 5, 1945: The first impression was that of myocardial infarction in a heart that already had one incident of thrombosis several years ago. There are several inconsistencies to be explained: (1) Marked ileus (this was present throughout the entire illness and was refractory to treatment); (2) involvement of the upper lobes of both lungs when one expects the lower lobes to be involved in a heart case; (3) bizarre x-ray of the chest exhibiting multiple small deposits throughout both lungs; (4) thick bloody sputum from which were obtained pneumococcus type III, Staphylococcus albus, and Streptococcus hemolyticus. The x-ray findings are not those of pneumonia or infarct, rather they suggest the possibility of carcinosis of the lungs."

It is my opinion that the slightly increased blood amylase activity in this case was due to the superimposed pneumonitis. Increased blood amylase activity in pneumonia has been reported (12, 14, 15). The mechanism is difficult to explain but the following factors, alone or in combination, may act to produce this effect in pneumonia: (1) The pneumococcus capsule is a polysaccharide. It is conceivable that this substance which has been labelled "SSS" (specific soluble substance) may call forth an added amount of amylase in the blood stream. I was unable to prove this (14). (2) There may be pressure by the congested lungs upon the thoracic lymph duct and this may increase the blood amylase activity. (3) The infection itself may involve other organs so that it is conceivable that in pneumonia we may have a mild pancreatic edema which in turn will increase blood amylase activity. The fact remains that in 2 of every 3 cases, an increased blood amylase activity was found in pneumonia (14).

Case 79086, with a diagnosis of toxic nodular goiter and diabetes mellitus is of interest because Bartlett has reported a decreased blood amylase activity in thyrotoxicosis, and he believes that such a decrease is indicative of liver damage. This one case showed a slightly increased blood amylase activity, the test being run off with a water control (16) because of the associated diabetes mellitus. Among the many laboratory findings were two basal metabolic rates of plus 79 per cent and plus 92 per cent. Suffice it to state that I am not sure how wise it is to draw any conclusions from blood amylase activity in thyroid disease. The experimental work of Cope and associates on dogs and rabbits produced variations in serum amylase which were not consistent.

Nothing can be said about case No. 80300, a white female, aged 56, who was admitted December 28, 1944, and who signed her own release January 5, 1945. Her important manifestations were diffuse vague abdominal pain, vomiting, tenderness over the entire abdomen without rigidity, more pronounced in the right hypochondrium. Her blood Wassermann was positive. Her blood amylase activity was slightly increased.

In summing up this analysis of the 9 cases of group 3 in which a slightly increased blood amylase activity was found, it appears safe to state that the pancreas is only secondarily and mildly involved in certain clinical enti-

ties. In cases in which it is doubtful as to whether or not the pancreas represents the principal seat of pathology, blood amylase activity determinations should be made repeatedly, every day or every other day. Ordinarily, a careful analysis of the clinical and laboratory findings will lead one to a correct diagnosis.

Group 4. In group 4 there were 7 cases with moderately increased (3 plus) blood amylase activity. These 7 cases represent 10.1 per cent of the 69 patients observed. In every one of the 7 cases the pancreas appeared to be involved. This was proved in 3 instances, case Nos. 72495, 79855, and 82077 which are reported in detail in the fore part of this paper. I was unable to trace Cases F. F. and F. S. so I have considered them as not proved.

Case No. 79627 was studied carefully and a final diagnosis of duodenal ulcer, proved by x-ray and other acceptable criteria, was made. Because of the close proximity of the duodenal lesion to the pancreas, one should not be surprised to find pancreatitis associated with duodenal ulcer. This patient improved on conservative treatment and her blood amylase activity was then found to be normal. This case and case No. 78148 in group 5 tend to corroborate the findings of Probstein, Wheeler, and Gray and those of Goyena and Cipolla who reported increased blood amylase activity in gastroduodenal ulcers. Probstein, *et al.* found blood amylase activity normal or subnormal when the lesion was on the anterior wall of the stomach, moderately elevated when it was on the posterior wall of the stomach. They believe that such findings are of value in differentiating such lesions from acute pancreatitis. On the other hand Hinton found blood amylase activity determinations of little value in 40 cases of peptic ulcer; and Lewison found the blood amylase activity elevated in only 2 of 25 cases of peptic ulcer.

Case No. 74866, a white male, aged 71 years, was admitted October 2, 1943, and discharged October 6, 1943, improved. The chief manifestations were severe abdominal cramps associated with diarrhea. The onset was sudden, at 2:00 a.m., October 1, 1943. He went to work but had to call a physician at 9:00 a.m. He was sent to the hospital for observation. There was no history of previous medical or surgical diseases. On physical examination his temperature ranged between 101 and 103 degrees F. (38.3° and 39.4° C.). There was marked abdominal tenderness and spasticity in the epigastric and left hypochondriac areas. The clinical impression was acute pancreatitis or perforated viscus. X-ray examination of the abdomen revealed no evidence of intestinal obstruction or ruptured viscus. The *blood amylase activity* was moderately increased on October 2 (the day of admission), and it was again found moderately increased 2 days later. The patient improved on conservative therapy and was discharged October 6, 1943, 4 days after admission, with a final clinical diagnosis of acute pancreatitis.

Of the 3 proved cases of pancreatitis (case Nos. 72495, 79855, and 82077) 2 died. We are thus left with the impression that a moderate increase in blood amylase activity may be associated with a serious prognosis. One should not be surprised that a greater blood amylase activity is not found in acute hemorrhagic pancreatitis. In case No. 79855, there was grossly no viable pancreatic tissue left. In case No. 73196, group 5, only the head of the pancreas exhibited viable pancreatic tissue (see Fig. 2).

The study of these 7 cases in group 4 has led me to believe that a moderate blood amylase activity is almost always associated with pancreatitis of serious import and should be so considered until proved otherwise.

Group 5. In group 5 there were 9 cases with markedly increased (3½ to 4 plus) blood amylase activity (13.1 per cent of the 69 patients observed). Four of these cases (Nos. 73196, 76131, 76645, and 364105), reported in detail in the fore part of this paper, were proved at operation or at necropsy.

Case No. 74626 was a white male, aged 57 years, who was admitted September 9, 1943, with a chief complaint of pain in the right upper quadrant associated with vomiting. He had had a cholecystectomy 1 year before and was well until the sudden onset of his present illness. His abdomen was very much distended and there were marked tenderness and spasticity in the right upper quadrant. A clinical diagnosis of intestinal obstruction was made. The patient signed his own release the same day but was readmitted the following day, September 10, 1943, with the same complaints plus intense icterus. Among the laboratory findings was found a *marked increase in blood amylase activity.* A diagnosis of acute pancreatitis was made and the patient improved under conservative therapy. Three days later his *blood amylase activity* was normal (2 plus). The following day, September 14, the *blood amylase*

activity was slightly increased. On September 17, the patient had another bout of abdominal pain and vomiting and on that day the *blood amylase activity* was found moderately (3 plus) increased. The patient improved again under conservative treatment and signed his own release on September 20, 1943.

This case demonstrated how well the blood amylase activity parallels the clinical course of acute pancreatitis. There is little doubt in my mind that this was a true case of acute pancreatitis though I have recorded it as an unproved case, because operation was not performed and the pancreas, for that reason, was not actually visualized.

Case No. 75622, a white female, aged 66, was admitted December 1, 1943 and discharged December 22, 1943, improved. Her chief complaint on admission was pain in the stomach for 2 weeks and vomiting for the past 2 days. With the onset of the abdominal pain she suffered a right-sided hemiplegia and developed a severe headache. Her past history disclosed that she had had an attack of gall-bladder colic 6 years before. Otherwise her health had been good. On physical examination her temperature was 100 degrees F. (37.8° C.), pulse 108, respirations 24, blood pressure 180 millimeters mercury systolic, 80 millimeters mercury diastolic. Her abdomen was tender in the right upper quadrant. The liver could be palpated a handbreadth below the costal margin. Both lower extremities exhibited ulcers. The reflexes on the right side were hyperactive. The laboratory findings were as follows: Urine—specific gravity 1.019; albumin, negative; sugar 3 plus; a few white blood cells; no red blood cells; no casts; acetone, negative. Icterus index was 20; cholesterol 235 milligrams per cent; white blood cells 11,800, with polymorphonuclear leucocytes 76 per cent, lymphocytes 20 per cent, mononuclear leucocytes 4 per cent; blood sugar 210 milligrams per cent; *blood amylase activity* markedly (4 plus) increased. For one reason or another no attention was paid to the blood amylase activity and a clinical diagnosis was made of acute cholecystitis, mild apoplexy, and diabetes mellitus. The patient was treated conservatively though the surgeon who was called in consultation recommended cholecystectomy, his diagnosis being cholecystitis. The patient was discharged, improved, without operation, December 22, 1943.

In reviewing this case I cannot escape the impression that the patient's chief complaints were due in part, at least, to acute pancreatitis. And I am forced to conclude that a marked degree of blood amylase activity increase is not necessarily related to a serious prognosis. The clinical status of the patient is a far better guide to prognosis.

Case No. 76140 is of interest because the blood amylase activity determinations were made twice, on the 7th and 8th days *post-operative* to see what it would show. On both occasions the *blood amylase activity* was markedly (3½ plus) increased. The operation was performed January 20, 1944, and consisted of a gastrectomy and splenectomy. The patient developed pneumonia and anuria and expired on January 28, 1944, 8 days after operation.

The patient in this case was a white male, aged 53 years, who had had stomach trouble for the previous 2 years and had lost 25 pounds (11.4 kgm.) in that time. His previous health had been good. The physical examination among other things disclosed a hard nodular mass in the epigastrium, a mitral systolic murmur, and marked varicosities in the left popliteal fossa.

At operation the stomach had to be shaved away from the pancreas to which it was strongly adherent. Bleeding occurred at the lower pole of the spleen, and it was deemed necessary to remove the spleen along with the stomach.

In reviewing this case one regrets that a blood amylase activity determination was not made prior to operation. So many possibilities present themselves in this case as a cause for the increased blood amylase activity after operation that any one, or combination, of the following factors could easily have been the responsible factor: (a) injury to the pancreas and spleen (11); (b) the postoperative pneumonia; (c) the anuria. There was no necropsy. The pathologic diagnosis (by Dr. A. J. Gitlitz) was infiltrating adenocolloid carcinoma of the stomach with carcinomatous lymphangitis and lymph node metastases; mild toxic splenitis.

The seventh case in group 5, a white male, aged 65, was admitted three times in 1944 (history Nos. 77790, 78099, and 79261). On first admission, May 27, 1944, the patient had an incarcerated right inguinal hernia, which was operated upon the same day and he was discharged, recovered, June 14, 1944. On second admission 4 days later, June 18, 1944, he came with a chief complaint of right upper quadrant pain and icterus. An electrocardiogram showed no evidence of a heart lesion and an x-ray film of heart and lungs revealed no lung pathology. The heart was considered normal in size and configuration. The *blood amylase activity*, the day after this admission, June 19, 1944, was *markedly (4 plus) increased*. He was treated conservatively and discharged, improved, July 11, 1944, with a final diag-

nosis of acute pancreatitis. On third admission, September 24, 1944, a diagnosis of arteriosclerotic heart disease was made. He expired October 27, 1944. Roentgenograms of the chest after lipiodol injection showed no evidence of bronchiectasis. The right dome of the diaphragm was elevated and there was air between the liver and the diaphragm. Examination of the esophagus showed a filling defect at the level of the arch of the aorta and a dilatation proximal to this point. Below the filling defect there was a constriction, and the barium trickled slowly past this area. Esophagoscopy was performed by Dr. L. Markowitz, and a portion of the lesion was obtained for biopsy October 24, 1944. The pathologic report was squamous cell carcinoma with pearl formation. The patient expired October 27, 1944. There was no necropsy.

It is my conviction that on the second admission of this patient the diagnosis was acute pancreatitis. I have not considered this a proved case because neither operation nor necropsy was performed and the pancreas, for those reasons, was not visualized. Once again we note that a marked blood amylase activity need not necessarily spell a serious prognosis with regard to acute pancreatitis. It is the clinical status of the patient, rather than the laboratory aid, that is the surest guide to prognosis.

Case No. 78148 in group 5, a white male, aged 64 years, was admitted June 21, 1944, and discharged July 6, 1944, improved. His chief complaint was right upper quadrant pain which radiated to the left across the abdomen. The pain was of 8 weeks' duration. His temperature ranged between 98.6 and 100.6 degrees F. (37.0° and 38.1° C.), pulse 68 to 100, respirations 20 to 24. The laboratory work-up included the following: gastrointestinal x-ray revealed duodenal ulcer. The white blood cells numbered 14,050 with stab forms 6 per cent, polymorphonuclear leucocytes 60 per cent, lymphocytes 33 per cent, monocytes 1 per cent; hemoglobin was 16.5 grams per cent. Red blood cells numbered 5,220,000. Blood sugar was 500 milligrams per cent; nonprotein nitrogen was 26 grams per cent. Urine showed specific gravity 1.042; albumin, negative; sugar, 3 plus; acetone, a trace; an occasional white blood cell; no red blood cells; casts, none. The *blood amylase activity* was markedly (4 plus) increased. The patient was treated conservatively by means of a diabetic diet and the injection of protamine zinc insulinate. He improved and was discharged July 6, 1944.

Since a water control (16) was not run when the blood amylase activity was determined, it is not known how much of the cuprous oxide precipitation was due to the high blood sugar. Experience has taught that a marked blood amylase activity in diabetes mellitus is not entirely due to the free blood sugar when the cuprous oxide precipitation method is used. In this case there was a proved duodenal ulcer, and it is likely that the abdominal pain was due to a mild pancreatitis induced by the nearby duodenal lesion. However, one can only speculate about this in this case, since a water control was not run to determine how much of the cuprous oxide precipitation was due to the free blood sugar in this severe diabetic. Goyena and Cipolla and others have shown that there is an increased blood amylase activity in some cases of duodenal ulcer. Our 2 cases, case No. 79627 group 4 and case No. 78148 group 5, tend to corroborate these findings.

In summing up on group 5 the conclusion is arrived at that a marked blood amylase activity always indicates involvement of the pancreas but that *it does not always* indicate that the pancreas is the main seat of the pathology. The outstanding exceptions were in the case of superior mesenteric vein and portal vein thrombosis, in duodenal ulcer, and in carcinoma of the stomach where the lesion is on the posterior wall adherent to the pancreas. Of the 3 proved cases in which the pancreas was the main seat of the pathology, only 1 died. We are thus reminded that a marked blood amylase activity in acute pancreatitis does not necessarily mean a serious prognosis.

In Table I, 6 cases of pancreatitis proved at operation or at necropsy have been grouped in order to emphasize the fact that the introduction of a laboratory aid, such as the cuprous oxide precipitation test for the determination of blood amylase, is fraught with difficulties. In Cases 1 and 4 of this table the test was run after operation, *after* the diagnosis was established. This sort of finding is always anticlimactic. In Case 2, a normal blood amylase activity was found and subsequent operation showed the presence of pancreatitis. This, to say the least, is always disappointing in spite of the fact that it is well known that blood amylase tends to decrease to normal when pancreatitis is subsiding, *and does so rapidly*.

In 3 cases the blood amylase activity was determined before operation or before nec-

TABLE II.—THE PRINCIPAL PATHOLOGY AND BLOOD AMYLASE ACTIVITY IN 69 CASES

Principal pathology	No. of cases	Blood amylase activity		
		Normal	Decreased	Increased
Pancreas	12	1	0	11
Gall bladder	15	10	1	4
Gastrointestinal	16	11	1	4
Retroperitoneal and mesenteric	4	1	0	3
Aortic aneurysm	2	1	0	1
Thyroid	1	0	0	1
Liver	8	7	1	0
Kidneys	3	3	0	0
Pulmonary tuberculosis	5	1	4	0
Miscellaneous	3	2	0	1
Total	69	37	7	25
%	100	53.6	10.1	36.3

ropsy and in all 3 (cases Nos. 3, 5, and 6) pancreatitis was found.

Two conclusions have been drawn from this study: (1) When increased blood amylase activity is found pancreatitis should be deemed to exist unless proved otherwise; (2) if one is to make a correct diagnosis of pancreatitis before operation or before necropsy, one must be pancreatic disease conscious.

In Table II are given the principal pathology and blood amylase activity in 69 patients. A study of this table has led to the conclusion that multiple pathology is the rule rather than the exception when pancreatitis is part of the picture. In 25 cases (36.3%) there was an increased blood amylase activity. In 7 cases (28% of the 25, 10% of the entire series of 69 cases) the pancreas was the principal seat of pathology as proved at operation or by necropsy.

In only 1 case (2.3%) of the 44 cases in which the blood amylase activity was normal or decreased was a proved pancreatitis found. Thus again I am forced to conclude that a normal or decreased blood amylase activity tends to rule out pancreatitis or that, when it is thought to be present, then it is subsiding or has subsided. By the same token, whenever an increased blood amylase activity is found pancreatitis should be deemed to exist unless proved otherwise. A careful evaluation of all the facts will most surely lead to a correct diagnosis.

In estimating the number of cases in which the test was used to include or exclude pancreatitis the 5 cases of tuberculosis and the 1 case of toxic nodular goiter were not counted. Thus there were 63 cases in which it was sought to include or exclude pancreatitis. Of these a clinical diagnosis of pancreatitis was made in 12 (19%) cases of which 7 (11%) were proved at the time of operation or necropsy.

This is significant. It implies that every patient with upper abdominal pain must be considered suspect with regard to pancreatitis. If one keeps pancreatitis in mind at least 11 proved cases of pancreatitis may be discovered in every 100 patients with upper abdominal pain. And the more cases of pancreatitis that are found the better will be our treatment, the better will be our results.

Of the 6 proved cases of pancreatitis 3 patients (50%) died. Of these, 2 cases were fulminating affairs. As one reviews the histories in these cases the impression is gained that time is lost in making an accurate diagnosis and that there is as yet no set plan of treatment which has been found uniformly effective. Reflection upon this leads me to suggest that a "pancreatitis team" be formed in each hospital to cope with this problem and that there be a central "pancreatitis registry" where all proved cases of pancreatitis could be filed and made available for study and evaluation of the manifold phases of this truly serious disease.

With the advent of penicillin it is likely that more patients with acute pancreatitis will recover if the diagnosis is made early. But, in the presence of acute hemorrhagic pancreatitis or pancreatic necrosis, it strikes me that only a careful combination of medical and surgical treatment will cut down the mortality rate. I feel reasonably certain that the hospital staff that is pancreatic disease conscious will produce the best end-results.

In the following tabulation have been included the clinical entities in which blood amylase activity has been found to be increased or decreased.

Increased	Decreased
1 Acute pancreatitis, trauma of the pancreas and spleen, pancreatic collections (pseudocysts)	1 Pernicious anemia
2 Pneumonia, in 2 out of every 3 cases	2 Pneumonia and other infections
3 Perforation of peptic ulcer into or near the pancreas	3 Obstructive jaundice
4 Duodenal ulcer	4 Primary and secondary malignancy of the liver and bile ducts
5 High intestinal obstruction	5 Impaired renal function where there is a great loss of albumin
6 Salivary duct occlusion, suppuration, or mumps	6 Diabetes mellitus
7 Impaired renal function	7 Toxemia of pregnancy
8 Superior mesenteric vein and portal vein thrombosis	8 Drug poisoning
9 Common bile duct obstruction	9 Burns, with liver and loss of plasma protein
10 Adenocarcinoma of the gall bladder	10 Acute alcoholic state of the chronic alcoholic
11 Toxic nodular goiter	11 Hyperthyroidism, with impaired liver function
12 Mesenteric cyst	12 Tuberculosis
13 Retroperitoneal metastases	13 Hemorrhagic shock
14 Aneurysm of thoracic aorta	14 Perforation of peptic ulcer, anterior gastric wall
15 Adrenal insufficiency in the dog	

By and large a careful analysis of any given case will lead one to a correct diagnosis if one keeps pancreatitis in mind. Just the mere fact of thinking about pancreatitis is almost in itself sufficient. The laboratory aids are helpful, indeed, but one should not readily discard his years of clinical experience when a laboratory aid fails to corroborate a clinical impression.

GENERAL COMMENTS

At the beginning of this article it was stated that blood amylase activity determinations have been used with *increasing* success at our hospital for over 4 years. The cuprous oxide precipitation test itself is truly reliable but its successful evaluation varied at first for one or more of the following reasons:

1. Difficulty was encountered in making the medical staff pancreatic disease conscious. Now, however, after 4 years the test is being ordered with fair regularity in cases characterized by upper abdominal distress. The greatest comfort is derived when the report is normal or decreased blood amylase activity.

2. Difficulty was encountered in getting the medical staff to realize that while an increased blood amylase activity nearly always implied pathologic involvement of the pancreas *it did not always imply that the principal pathology lay within the pancreas.* Thus a marked increase in blood amylase activity has been reported in the pneumonias (12, 14, 15), in duodenal ulcer (6, 18), in acute trauma of the spleen (11) and in mesenteric vein and portal vein thrombosis reported herein. A careful evaluation of the history and physical findings in each case will almost always lead one to a correct diagnosis.

3. Difficulty was encountered in gaining the confidence of the staff in a gross evaluation of blood amylase activity in terms of normal, increased, decreased, or by plus and minus signs. In another article (14) I have gone at length into my reasons for adopting a gross measure of amylase activity. Suffice it to state that, after having performed this test more than 500 times, I am more than ever convinced that measurement of blood amylase activity by means of cuprous oxide precipitation is a quick, simple and reliable method. Anyone may perform the test. It does not take highly trained technicians and it requires only the simplest of apparatus.

SUMMARY

1. Moderate to marked blood amylase activity is almost always associated with disease of the pancreas.

2. Normal or decreased blood amylase activity almost always excludes pancreatitis. Where pancreatitis exists in conjunction with a normal or decreased blood amylase activity it may be safely assumed, if the clinical status of the patient bears it out, that the pancreatitis has subsided or is subsiding.

3. A slightly increased blood amylase activity may be safely regarded as indicating pancreatic involvement secondary to principal pathology elsewhere. When in doubt, tests should be repeated every day or every other day if the condition of the patient permits.

4. The presence of multiple pathology is the rule rather than the exception in acute pancreatitis. Biliary tract disease is the commonest complicating factor in this respect. An attack of acute pancreatitis may be the first clinical sign of the presence of biliary

tract disease. And the known presence of biliary tract disease, when associated with a bout of epigastric pain, may make the clinician forget that the pain may be due to acute pancreatitis. In acute pancreatitis a history of repeated attacks of epigastric pain, sometimes dating back several years, may be obtained in almost every case.

Because of these observations more and more blood amylase activity determinations are being made at our hospital in cases in which the chief complaint is epigastric pain or distress. As a result, more and more cases of pancreatitis are coming to light.

5. Decreased or absent blood amylase activity in this series of 69 cases was in no instance associated with acute pancreatitis. The liver is considered by some observers to be one of the main sources of blood amylase. For that reason a decreased or absent blood amylase activity may be interpreted as evidence of impaired liver function. When so interpreted, the test should be corroborated by other well known liver function tests.

CONCLUSION

There is no short cut to the diagnosis of acute pancreatitis. In spite of all difficulties encountered in the evaluation of blood amylase activity, blood amylase activity determinations remain as a definitely valuable aid in the diagnosis of acute pancreatitis.

REFERENCES

1. Bartlett, W., Jr. Surgery, 1938, 3:201. Tr. Am. Ass. Study Goiter, 1938, p. 494.
2. Colp, R., Gerber, I. E., and Doubillet, H. Ann. Surg., 1936, 103: 67.
3. Cope, O., Kapnick, I., Pratt, T. D., Lambert, A., and Volut, M. G. Endocrinology, 1939, 25: 236, 238.
4. Dozzi, D. L. J. Lab. Clin. M., 1940, 25: 1303.
5. Dragstedt, L. R., Haymond, H. E., and Ellis, J. C. Arch. Surg., 1934, 28: 232–291.
6. Goyena, J. R., and Cipolla, E. An. Inst. Clin. Méd., 1943, 1: 521–527.
7. Hinton, J. W. Arch. Surg., 1934, 28: 580.
8. Johnson, T. A., and Bockus, H. L. Arch. Int. M., 1940, 66:62.
9. Lewison, E. F. Surg. Gyn. Obst., 1941, 72: 202.
10. McCorkle, H., Goldman, L., and Cornell, R. N. Clinics, 1942, 1: 756–771.
11. Naffziger, H. C., and McCorkle, H. J. Ann. Surg., 1943, 118: 594–602.
12. Nonaka, Y. Tokio Igakkai Zasshi, 1939, 53:971.
13. Pinkham, R. D. Surg. Gyn. Obst., 1945, 80: 225.
14. Polowe, D. Am. J. Clin. Path., 1943, 13: 288–301.
15. Polowe, D. Personal communication to Ludvig Hektoen, Chairman, Committee on Scientific Research, Am. M. Ass., May 3, 1933.
16. Polowe, D., Ratish, H. D., and Bullowa, J. G. M. Am. J. Clin. Path., 1942, 12: 62.
17. Popper, H. L., and Necheles, H. Proc. Soc. Exp. Biol., N. Y., 1941, 68:232.
18. Probstein, J. G., Wheeler, P. A., and Gray, S. H. J. Lab. Clin. M., 1939, 24: 449.
19. Somogyi, M. J. Biol. Chem., 1938, 125: 399.
20. Weiner, H. A., and Tennant, R. Am. J. M. Sc., 1938, 196: 167–176.
21. Wolfer, J. A. Surg. Gyn. Obst., 1931, 53: 433.

AMINO ACIDS IN THERAPY OF DISEASE

Parenteral and Oral Administrations Compared

S. C. MADDEN, M.D., S. H. BASSETT, M.D., J. H. REMINGTON, M.D.,
F. J. C. MARTIN, M.D., R. R. WOODS, M.D., and F. W. SHULL, M.D.,
Rochester, New York

AMINO acids were tested for their value in the treatment of human disease in the observations presented in this paper. Certain mixtures of those amino acids reported essential for the growth of rats (25) together with the amino acid glycine were given over long periods of time either parenterally or orally. *Parenterally* they were of considerable value (Tables I and III), providing nitrogen balance, weight gain, and clinical improvement. Similar benefit has been previously shown in man (4) and in dogs (17, 20). *Orally* they maintained nitrogen balance (Table II) but in the 1 patient studied they were not quite so well utilized as were natural food proteins.

Nitrogen balance with 8 amino acids has been obtained in normal human beings (26). These 8 are threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, and methionine. The mixtures used in the observations of this paper contain in addition to these 8 amino acids histidine, arginine, and glycine. It appears in Table I that histidine may be required for nitrogen balance in a patient with chronic ulcerative colitis. In normal man histidine has been omitted and nitrogen balance maintained (26, 2).

Parenteral nitrogen feeding in man was first successfully reported only 6 years ago (12). Parenteral feeding is indicated and important in treatment when feeding by the gastrointestinal route is impossible or inadvisable. A very high protein intake with its beneficial results, such as obtained by natural diet in the patient of Table IV, would be very difficult of achievement by wholly parenteral means. Nor should it be attempted until real efforts to improve the oral intake have failed. Complete and successful parenteral administration of protein nitrogen, fat, carbohydrate, and accessories has been achieved in man (8).

The studies here involving parenteral feeding were not intended to provide complete nutrition parenterally. It was desired to test amino acid mixtures given parenterally while optimum quantities of nonprotein dietary constituents were given orally. In most of the observations given in Tables I to III there was some protein present in the diet; but in 2 periods presented in Table III the intake was almost exclusively from amino acids.

From the Departments of Pathology and Medicine, the University of Rochester School of Medicine and Dentistry.

GENERAL MATERIALS AND METHODS

All metabolism studies were made with the patient in the metabolism division, except for the study presented in Table II. Food and fluid net intakes were carefully weighed or measured and their nitrogen contents calculated from standard reference tables. The nitrogen content of some of the diets as noted in the clinical histories was checked by Kjeldahl analysis of a complete day's intake. All urine, feces, and vomitus were saved for analysis. Stool collection periods were marked by tomato seeds given on the first day of the period. Total nitrogen was done by macro-Kjeldahl procedure and urea plus ammonia nitrogen by the method of Van Slyke and Kugel. The patients were weighed under uniform conditions on a special balance, and weights at ends of periods noted (see tables).

The *amino acid mixtures* were somewhat similar to those used in the first patient (4). Mixture designated vuj contained in grams per 100 gram dl-threonine 10.8, dl-valine 13.8, l(-)-leucine 15.4, dl-isoleucine 10.8, l(+)-lysine. HCl. H_2O 12.3, dl-tryptophane 1.8, dl-phenylalanine 6.9, dl-methionine 6.2, l(+)-histidine. HCl. H_2O 4, l(+)-arginine. HCl 8,

glycine 10; nitrogen content 13.6 per cent by calculation, 13.3 per cent by Kjeldahl. Mixture vuk is vuj with the 1(-)-leucine replaced by the same amount of dl-leucine. Mixture vu consists of dl-threonine 7, dl-valine 11, dl-leucine 18, dl-isoleucine 12, 1(+)-lysine. HCl. H_2O 12, 1(-)-tryptophane 4, dl-phenylalanine 12, dl-methionine 6, 1(+)-histidine. HCl. H_2O 4, 1(+)-arginine. HCl. 7, glycine 7; nitrogen by calculation 13.1 per cent. Mixture vua is vu with the dl-leucine replaced by 1(-)-leucine 9 gm. Mixture vub is vua with the phenylalanine reduced to 8 grams.

The amino acids were dissolved in distilled water just below the boiling point, filtered, and autoclaved for 15 minutes at 15 pounds pressure. The solutions were water clear, often faintly yellowish after autoclaving. They were acid, about pH 5 except as noted.

The amino acids were given intravenously or subcutaneously in 6 to 13 per cent concentration. The concentration and volume of each injection was measured and any small quantities not given because of incomplete drainage of tube or flask were deducted. The vuj, vua, and vub mixtures were usually given in 10 per cent concentration. Mixtures vuk and vu were given usually in 7 per cent solution. The solubility of the different mixtures has largely determined the concentration employed.

ANALYSIS OF DATA

The observations recorded in Table I represent an almost perfect metabolism study of 100 days' duration. The patient was intelligent and co-operative, and except for the loss of the fecal output of period 15 the measurements of nitrogen intake and output were complete.

Nitrogen balance and considerable weight gain were obtained during 85 days (periods 2 to 18) when amino acids furnished the bulk of the nitrogen intake—85 to 93 per cent except for periods 3 and 4 of about 80 per cent. Synthetic mixtures of the 10 amino acids essential for the growth of rats (25) and glycine provided this nitrogen, except for period 3 when the protein hydrolysate amigen was given. These amino acid mixtures included unnatural isomers of threonine, valine, isoleucine, tryptophane, phenylalanine, and methionine, and, in mixture vuk, leucine. *No toxicity to these unnatural isomers* was detected. The amino acid mixtures of period 2 produced clinical disturbances, and nitrogen balance was not obtained (Case 1, first study, Table I). Amigen in period 3, however, was well utilized and well tolerated at injection rates below 1.2 milligrams nitrogen per kilogram per minute. In period 4 the mixture vuj was similarly utilized and tolerated. It should be noted that the urinary nitrogen partition is the same with this mixture containing unnatural isomers as with amigen. With either material the undetermined fraction is higher than with oral feeding of natural protein (compare with period 1). A similar difference between intravenous and oral administration of digests to dogs has been found (19).

The *oral feeding* periods 12 to 14 are of much interest. Nitrogen retention was considerably greater than in the injection periods. This retention was associated with a reduction in the urea and ammonia nitrogen of the urine. In contrast to the observations in dogs (19) there was no decline in the undetermined urinary nitrogen. A *rise in fecal nitrogen* in periods 12 and 13 tapered off in period 14. An increase in the number of bowel movements also occurred, and as detailed in the case report, the number did not return to the previous level until period 17.

Tolerance was good but not strikingly greater for mixture vuj than for amigen in this patient. Better tolerance for other mixtures of amino acids was found in the observations of Table III and in the earlier report in man (4). Better tolerance for other mixtures has also been found in dogs (21, 18). In period 10 two of the intravenous injections were made in 13 per cent concentration, both without reaction or vein injury; the nitrogen rates, however, were only .7-.8 milligram per kilogram per minute.

The *improved tolerance* of the mixture *without phenylalanine* is quite definite in this patient, as described in Case 1, Table I, periods 6 and 7. Omission of histidine, arginine, lysine, or methionine was without noticeable effect on tolerance. *Subcutaneous injection* of the amino acid mixture in 10 per

TABLE I.—AMINO ACIDS PARENTERALLY WITH NITROGEN BALANCE, WEIGHT GAIN, AND CLINICAL IMPROVEMENT

M. E., aged 26 years, chronic ulcerative colitis

Period 5 days	Amino acids	Nitrogen intake per period		Nitrogen output per period				Nitrogen balance per period	Weight
		Food	Amino acids	Urine total	Urine urea-NH_3	Urine undetermined	Feces		
0		Grams	Grams	Grams	Per cent	Grams	Grams	Grams	Kilograms 52.26
1	None	101.5		49.5	81	9.3	39.7	+12.3	52.09
2	Varies, i.v.	6.5	68.0	68.3	72	18.9	26.5	−20.3	50.23
3	Amigen, i.v.	15.2	62.6	56.6	67	18.9	12.5	+8.7	53.63
4	Vuj, i.v.	15.2	59.9	55.7	69	17.4	14.7	+4.7	54.12
5	Vuj, i.v., s.c.	7.5	102.0	93.4	73	25.5	18.7	−2.6	52.18
6	Vuj, i.v., s.c.	13.9	85.6	82.4	69	25.3	13.6	+3.5	54.43
7	Vuj, i.v.	12.0	84.0	80.9	70	24.0	9.1	+6.0	53.43
8	Vuk, i.v.	7.4	85.9	76.2	68	24.5	13.9	+3.2	54.63
9	Vuk, i.v.	6.9	43.1	44.3	61	17.3	13.7	−8.0	55.91
10	Vuj, i.v.	6.9	43.1	37.0	60	14.9	13.8	−0.8	57.19
11	Vuj, s.c.	6.9	43.2	36.4	65	12.8	13.2	+0.5	58.19
12	Vuk, oral	6.9	43.3	25.1	49	12.7	17.0	+8.1	58.28
13	Vuk, oral	6.9	43.3	27.7	49	14.1	16.1	+6.4	59.09
14	Vuk, oral	6.9	43.3	27.4	48	14.2	13.8	+9.0	59.83
15	Vuk, i.v.	6.9	43.3	38.2	63	14.2	lost		60.08
16	Vuk minus histidine, i.v.	6.9	40.7	37.8	63	13.9	15.0	−5.2	60.78
17	Vuk minus histidine, i.v.	6.9	40.7	41.0	66	14.0	11.7	−5.1	61.27
18	Vuk, i.v.	6.9	43.1	36.2	61	14.2	12.0	+1.8	62.13
19	None	101.5		61.7	85	9.1	7.5	+32.3	62.50
20	None	101.5		65.0	87	8.3	11.5	+25.0	63.21

cent concentration during periods 5, 6, and 11 produced no disturbance and utilization was equal to that following intravenous injection (compare periods 10 and 11). It should be noted that this patient was an ambulatory, sensitive individual to whom these hypodermoclyses were no more uncomfortable than if physiological saline solution were being injected.

Improvement in clinical condition was evident by period 3 and continued throughout the study. The underlying disease was by no means cured, but its signs and symptoms were greatly alleviated. The number of bowel movements declined from 5 to 6 daily to 3 daily after only 5 days of parenteral nitrogen feeding. They were reduced to only 1 daily after period 6. *Marked reduction of fecal nitrogen* output was of equal interest (compare periods 1 and 6). Symptoms of abdominal distention also disappeared. Similar clinical improvement has been observed in another patient with chronic ulcerative colitis when given amigen intravenously and a high carbohydrate, low protein diet orally. Some of the clinical improvement in these cases may be due to the mental comfort of "special treatment," but probably not all of it.

Omission of histidine was associated during the second 5 days (period 17) with a *rise in urinary nitrogen*. Nitrogen balance was negative but it should be noted that nitrogen intake was less by the amount of the histidine nitrogen. We believe, however, that the rise in urinary nitrogen during histidine omission and its prompt return to the previous level upon histidine replacement indicates a requirement for histidine by this patient.

Weight increased steadily, particularly after period 7, and even during histidine omission. Nitrogen retention over the entire period of amino acid administration does not total enough to account for the large gain. Deposit of fat probably explains most of the increase. Weight increase continued without interruption when a natural diet was given during periods 19 and 20, now with large deposits of nitrogen, and the reduction in undetermined urinary nitrogen was striking.

CASE 1. First study. M. E. (SMH 203,158) was a 26 year old white painter with ulcerative colitis of 6 months' duration when the observations presented in Table I began. Two months previously he had left the hospital after a stay of 6 weeks. During this first admission no cause could be found for the colitis. Upon fluoroscopy the colon appeared large and its wall smooth. Upon sigmoidoscopy it showed many fine bleeding points but no distinct ulceration. Stools were 7 to 8 daily, a reddish liquid, half red blood cells and half leucocytes upon microscopic examination, but during bed rest, high protein and vitamin intakes, blood transfusions, and sulfasuccidine therapy, the number of bowel movements decreased to 3 to 4 per day. Out of the hospital some of this improvement was lost and the weight had declined from 58 to 52 kilograms. Upon the present (second) hospital admission it was suggested that a very low residue diet might be advantageous. After 6 days of routine care in the hospital the patient was transferred to the metabolism division. He remained ambulatory on the division throughout his stay.

In period 1 a soft "low residue" diet of natural foods was consumed. It provided daily protein 127 grams and calories 3104. The same diet was eaten during the last 2 periods (19 and 20) but during the intervening 17 periods a very low protein diet was given. The low protein diet varied somewhat until the eighth period and thereafter remained fairly constant. For the 10 periods (9 to 18) it consisted in grams, of orange juice 400, grapefruit juice 200, lemon juice 70, currant jelly 50, gum drops 200, sucrose 50, dextrose 235, corn starch 200, tapioca 10, cocoa 5, butter fat 40, cream (butter fat 36 per cent) 50, salt 2, baking powder 5. A corn starch-butter fat-tapioca "biscuit" was baked and corn starch-cream-fruit juice puddings were frozen. This diet contained by Kjeldahl analysis 1.38 grams nitrogen and a calculated 3,790 calories.

The actual caloric intake of the second period averaged 1,977 including the amino acids and of periods 3 to 7 varied between 3,200 and 3,500 including the calories from the amino acids (calculated as nitrogen $\times 25$). A vitamin B complex concentrate was given during the first 7 periods and thereafter a multiple vitamin emulsion (10 c.c. daily), described elsewhere (16). Sulfasuccidine 12 grams, ferrous sulfate 0.2 gram, and intramuscular liver extract (1 unit per c.c.) 2 cubic centimeters were all given daily during periods 8 to 20. On the bare possibility that insulin might encourage the appetite for the high carbohydrate diet 10 units was given 30 minutes before each meal beginning in period 8. The diet was fairly readily eaten.

During periods 2 to 18 amino acids were given as recorded in Table I. They were injected twice daily through period 8 and once thereafter.

In period 2 mixture vue (vub with dl-tryptophane) was first given, 43 grams in 30 minutes, and the patient became nauseated. He vomited during the next injection of 87 grams. The vu mixture, used at rapid rates without reaction in the observations of Table III, was then given, 50 grams in 105 minutes (1.2 mgm. nitrogen per kilogram per minute) without nausea and in 85 minutes (1.5 mgm. nitrogen per kilogram per minute) with nausea and vomiting. Nausea twice and vomiting once occurred with 3 of the remaining 6 injections. Vomitus nitrogen 1.5 grams was deducted from the intake in Table I.

In period 3 amigen (an enzymatic digest of casein and pork pancreas) in 5 per cent solution with 5 per cent dextrose was used. A total of 10.43 liters was given in 10 injections, the injections varying from 100 to 190 minutes in length. Only the one at 100 minutes (1.2 mgm. nitrogen per kilogram per minute) produced nausea.

In period 4 mixture vuj was given in approximately the same quantities (in 65 to 120 minutes per injection) with nausea on 2 occasions at 1.7 milligrams nitrogen per kilogram per minute. Dextrose, 5 per cent, was included in the amino acid solution during the period for more exact comparison with the amigen of period 3. During periods 4 to 6, the amino acid solution was adjusted to a *p*H of 6.5 by addition of sodium hydroxide—with no apparent effect on tolerance.

On each of the first 3 days of period 5 the large quantity of 195 grams vuj mixture was given with vomiting during 3 of the 6 injections. Omission of lysine, histidine, and arginine during one of these did not prevent vomiting. The amount given was reduced to half on the last 2 days; omission of methionine on 1 day did not prevent vomiting. These omissions of essential amino acids were associated with a weight loss from 54.12 kilograms at the beginning of the period to 52.18 kilograms at the end. Vomitus nitrogen of 3.5 grams was deducted from the intake in Table I.

In periods 6 and 7 mixture vuj 65 grams, was injected twice daily, usually once by vein and once subcutaneously. There was nausea on 2 occasions but usually no disturbance occurred when the rate was near 1 milligram nitrogen per kilogram per minute. On the last day of period 6 *phenylalanine* was omitted from both injections (by vein). There was no reaction to the injections given in 95 and 55 minutes, respectively, (2.5 and 2.6 mgm. nitrogen per kilogram per minute). The day's intake of phenylalanine when started 45 minutes after com-

TABLE II.—AMINO ACIDS ORALLY COMPARED WITH AMIGEN AND WHOLE EGG

M. E., aged 26 years, chronic ulcerative colitis

Period 10 days	Diet	Nitrogen intake per period		Nitrogen output per period				Nitrogen balance per period	Weight
		Amino acids	Basal	Urine total	Urine urea-NH_3	Urine undetermined	Feces		
		Grams	Grams	Grams	Per cent	Grams	Grams	Grams	Kilograms
1	Vuj	85.6	5.0	81.3	72	22.5	37.9	−28.5	58.6
2	Vuj	86.6	5.0	53.3	65	18.6	35.7	+2.6	59.3
3	Vuj	86.6	5.0	54.2	64	19.6	35.3	+2.1	59.5
4	Amigen	90.0	5.0	47.7	75	12.0	41.3	+6.0	59.8
5	Amigen	126.0	5.0	62.9	78	14.1	65.0	+3.1	59.5
6	Egg		87.9	40.6	73	11.1	57.6	−10.3	58.6

pletion of the second injection produced *nausea* at a rate of 0.6 milligram nitrogen per kilogram per minute.

When the mixture was given the next day (first day of period 7) with phenylalanine included, vomiting occurred at a total nitrogen rate of 1.7 milligrams per kilogram per minute, phenylalanine nitrogen rate of 0.08 milligram per kilogram per minute. The next day mixture vuj subcutaneously at 2.9 milligrams total nitrogen per kilogram per minute was followed by vomiting 45 minutes later. When phenylalanine was again omitted on the third day of period 7, the two injections (4 hours apart) were given by vein at 4.3 and 3.1 milligrams nitrogen per kilogram per minute without nausea or vomiting. The phenylalanine given 30 minutes after the second injection produced vomiting at the nitrogen rate of 0.3 milligram per kilogram per minute when 10.8 milligrams phenylalanine nitrogen per kilogram had been injected. The next day no reaction occurred to the complete mixture at 1.1 milligrams nitrogen per kilogram per minute, but 30 minutes after subcutaneous injection of the second dose at 3.6 milligrams nitrogen per kilogram per minute vomiting occurred. The vomitus nitrogen for period 7 amounted to 2.07 grams.

In period 8 the mixture was changed to vuk at the same intake level as in periods 6 and 7. No nausea or vomiting occurred at the slow of rates of 0.7 to 0.9 milligram nitrogen per kilogram per minute.

In periods 9 to 11 the amino acid intake level was reduced to half that of period 8 and injections were usually at the same slow rates even when given subcutaneously (period 11). At the end of period 9 and during part of period 10 the patient had for 3 days a sore, red pharynx and fever to 39.5 degrees C. It subsided uneventfully. Cultures were nonspecific.

In periods 12 to 14 the amino acids were given by mouth, the 10 per cent solution being mixed in the fruit juices and frozen puddings. After the first 2 days the patient stated that the taste was not unpleasant.

In period 15 the stool collection was accidentally discarded. Periods 16 to 20 were uneventful.

The patient's symptoms of abdominal discomfort subsided entirely during the early periods. The number of bowel movements decreased sharply during periods 1 to 7, the numbers per period being 27, 30, 17, 13, 10, 13, and 4, respectively. There was one stool a day during periods 8 to 11, but when the amino acids were given orally in periods 12 to 14 the numbers per period were 10, 9, and 8, respectively. During periods 15 to 18 the number declined again 9, 7, 5, 6, and in periods 19 and 20 on the same diet as period 1 were 3 only during each period. The stools did not become formed until the last two periods, and, although no blood or mucus was visible, still did not appear normal.

During the first 7 periods the plasma protein level rose from the region of 5.7 to the region of 6.3 grams per 100 cubic centimeters of plasma and remained there during the remaining periods except for dips to 5.8 during periods 10 and 11. The albumin:globulin ratio remained about 1.7 most of the time. The serum nonprotein-nitrogen, chlorides, and plasma carbon dioxide combining power varied within normal ranges. The hemoglobin rose from 11.1 to 13.2 grams while the red cell count remained at 4,200,000.

At the end of the study fluoroscopy showed improvement of the colon as compared with its appearance at the beginning of the study. Sigmoidoscopy, however, still showed bleeding points and excessive secretion in a reddened edematous mucosa. No ulcers were seen. The patient was discharged to work as a hospital orderly to be kept under observation. Subjectively and objectively he was temporarily greatly improved (Case 1, Table II).

In Table II the effects on nitrogen metabolism of giving *amino acids and amigen by mouth* are shown. The salutary effect on the symptoms of colitis in the observations of Table I suggested that an attempt to relieve these symptoms, which had recurred, should be made by oral administration of the amino acids. The symptoms were not relieved (Case

1, second study, Table II), but the observations are of interest.

The amino acids appear in this instance to be better tolerated by the intestine than amigen but amigen appears better utilized upon absorption from the intestine. These factors combine to yield approximately the same net retention of nitrogen in periods 2 to 5. The negative balance of period 1 probably reflects the change from the higher level of nitrogen intake which probably preceded the relatively low level of period 1.

The egg nitrogen of period 6, Table II, is better utilized than either the amigen or the amino acids, as judged by the relation of intake to urinary output, but the loss through the intestine offsets this advantage.

The weight remained fairly constant throughout the observations (Table II). The gain registered in Table I on similar intakes did not occur here probably partly because of increased caloric demand during activity outside of the hospital.

CASE 1. Second study. M. E. (SMH 203,158) was the same patient studied in the observations recorded in Table I. He worked for 1 week upon discharge from the hospital, then his old symptoms began to return gradually. Within 3 weeks he was having 8 to 9 bowel movements a day and soon had an acute febrile exacerbation. This gradually subsided during hospitalization and vigorous supportive therapy. During the first 2 months of this relapse his weight had declined to 47.6 kilograms but rose to 52 kilograms upon discharge from the hospital 2 weeks later. During the next 2 months he gained weight despite continuance of frequent loose stools.

As a co-operative out-patient he was eager to test the influence of the low residue diet again with amino acids by mouth, so that the conduct of the experiment was entirely satisfactory. The amino acids were weighed in the laboratory and the basal diet was weighed on a special balance at home. The basal diet for the entire 6 periods was identical with that of periods 9 to 18 (Table I) except for omission of the cream and the cocoa. It had a daily nitrogen content of 0.5 gram. The vitamin emulsion used was the same as that in the observations recorded in Table I. Urine was collected in 2 day periods under toluene with refrigeration, and analyzed the following day. Stools were collected in 10 day periods. The weight at the beginning of period 1 was 58.6 kilograms.

In periods 1 to 3 the amino acid mixture and the diet were completely consumed. Vomitus nitrogen the first day of period 1 was deducted from the intake. The acids without methionine were fairly innocuous to the palate, so that the patient took the methionine separately "as medicine," in divided doses to accompany the three meals a day.

In periods 4 and 5 amigen powder was dissolved and suspended in the diet, 75 grams daily in period 4, 100 grams in period 5 with 150 grams on the first day. It was tolerated although less palatable than the crystalline amino acids. An exacerbation of symptoms with abdominal pain and increased tenesmus and bleeding occurred during the last 2 days of period 4 and the first of period 5. Sulfasuccidine was then given for 6 days, and although the diarrhea increased for 4 days the other symptoms subsided.

The symptoms of colitis continued without relief during the 60 days of these observations. In fact the number of bowel movements rose from 8 to 10 daily prior to period 1, to 11 to 14 daily during period 1, totalling 120. During periods 2 to 6 the totals were 98, 111, 114, 145, and 124 respectively. The stools contained much mucus, and frequently blood.

In period 6 the protein intake came from 1 pound of hens' eggs daily (12 ounces on the first day). The nitrogen of the total diet of 1 day was determined by Kjeldahl analysis. On the fourth day of the period the patient had a transient upset and vomited once, nitrogen content 1.18 grams. He had lost his appetite for this stringent regimen by the close of the period and returned to his soft, more varied diet.

Table III further demonstrates the value in preoperative and postoperative care of parenteral feeding with amino acids. The patient, J.S., with chronic intestinal obstruction was maintained in positive nitrogen balance by intravenous and subcutaneous injection of amino acids, despite an intercurrent acute infection during periods 1 and 2. Moreover, during period 1 the nitrogen intake was entirely from amino acids except for 0.6 gram on 1 day only.

When no amino acids were given during period 4, the patient was unable to maintain adequate nutrition by mouth. Operation on the last day of this period corrected the obstruction (Cases 2 and 3, Table III).

Postoperatively J.S. (period 5) had an uneventful course and recovered rapidly. Nitrogen balance was maintained despite the serious injury of a major operation. The day-by-day balances of period 5, if one assumes equal division of fecal nitrogen, were +3.0, -0.4, -1.9, +2.4, and +2.7 grams, respectively. This is not the usual postoperative course of the nitrogen balance (10, 7, 15) but allowance must be made for the fact that the patient was emaciated. With zero intake of nitrogen the balance will obviously be negative in any case.

TABLE III.—AMINO ACIDS PARENTERALLY YIELD NITROGEN BALANCE AS SOLE SOURCE OF NITROGEN

Period 5 days	Amino acids	Nitrogen intake per period		Nitrogen output per period				Nitrogen balance* per period	Weight
		Amino acids	Basal	Urine Total	Urine urea-NH_3	Urine undetermined	Feces		
		Grams	Grams	Grams	Per cent	Grams	Grams	Grams	Kilograms
J. S., aged 21 years, chronic ileitis									
1	Vu, iv, sc	130.0	0.6	108.4	57	46.1	11.2	+8.4	38.9
2	Vu, iv, sc	65.2	3.4	64.7	60	25.8	5.8	−1.9	
3	Vu, iv	65.3	8.3	54.0	57	22.9	11.8	+6.6	38.6
4	None(Operation)	0	16.5+	22.1	76	5.4			37.1
5	Vu, iv	91.7	2.2	82.1	61	31.9	6.0	+5.8	
6	None	0	78.3	31.6	79	6.6	10.3	+36.4	37.2
H. S., aged 55 years, carcinoma of head of pancreas									
1	Vua, iv, sc	59.2	0.2	68.4	76	16.5	4.7	−14.8	60.4
2	Vub, sc	58.3	0.0	52.3	68	16.7	6.3	−1.8	

*Nitrogen of vomitus and Wangensteen drainage deducted.

If the nutrition is relatively normal preoperatively the balance will be markedly negative postoperatively. If the patient is protein depleted before operation the negative balance is much less (6). With moderate caloric and protein (or amino acid equivalent) intake balance can be maintained in such depleted individuals, as demonstrated in the present instance. Previously normal individuals require larger intakes of nitrogen, or possibly special kinds of nitrogen (18, 9).

Patient H.S., Table III, presented the difficult problem of nutrition in a jaundiced patient after a major operation. Anorexia and vomiting were severe and the superficial veins were very difficult to use for injection purposes. All but 2 of the 20 injections during the 10 days of study were made subcutaneously. Tolerance was good to the 10 per cent amino acids subcutaneously and on 2 occasions injections of more than 12 per cent concentration were given in period 2 without the slightest upset.

Nitrogen balance was approximated in the 2nd period with patient H.S., Table III, when the entire nitrogen intake was being provided by amino acids. The undetermined urinary nitrogen fraction was proportionately lower with mixtures vua and vub (as well as with vuj, Table I) than with vu. This may be indirect evidence of poor utilization of the unnatural d(+)-leucine contained in the vu mixture. Some conversion of d(+)-leucine into the l(-) form occurs in rats (23).

CASE 2. J.S. (SMH 199,516) was a 21 year old, white, college student with recurrent episodes of abdominal pain and vomiting during the past 7 years. He was emaciated and pale, weight 35.5 kilograms, height 175 centimeters. He had never shaved but his sexual development appeared normal. Fluoroscopy following barium showed several dilatations of ileum which were followed by an apparent obstruction.

To attempt to improve the condition of the patient before operation, he was transferred to the metabolism division 4 days prior to period 1, Table III for special diet control. Further oral feeding was tried the first 3 days on the metabolism division but vomiting of large amounts of fluid and food occurred every evening. The weight was raised to 37.4 kilograms 2 days before period 1 began, largely by retention of saline infusions. A Miller-Abbott tube was passed into the jejunum the day before period 1 and distention was relieved, but vomiting of ingested food and fluid persisted. An aphthous stomatitis, pharyngitis, and esophagitis began the day before the tube was passed and continued during periods 1 and 2.

In period 1 the amino acid mixture vu, 200 grams, was given daily and the caloric and vitamin intakes were provided by a fortified lemonade and synthetic vitamins and concentrates. There was no clinical disturbance which could be attributed to the amino acids. Fever between 38 and 39.5 degrees C. accompanied the stomatitis and near the end of the period an area of patchy density by x-ray was found in the right lower lobe. Sulfadiazine was given with questionable benefit.

The average daily caloric intake was 1,890. Other pertinent laboratory data were plasma protein 4.0 grams per 100 cubic centimeters plasma, nonprotein nitrogen 23 milligrams per 100 cubic centimeters serum, chlorides 107 milliequivalents per 100 cubic centimeters serum, carbon dioxide combining power 41 volumes per 100 cubic centimeters plasma, hemoglobin 9.5 grams per 100 cubic centimeters blood, leucocyte count 8,600 per cubic millimeter blood. The nitrogen in the vomitus and Wangensteen drainage amounted to 2.6 grams.

In period 2 the amino acid solution was modified on one day by addition of sodium carbonate of sodium content chemically equivalent to the chloride content of the amino acids. The resulting solution had a reaction of pH 8.45 and after subcutaneous injection of 100 grams amino acids in 1600 cubic centimeter solution the patient's thighs were sore and reddened and a small blister appeared at the site of the needle puncture. This irritation subsided without further progression. All other injections at the usual acid pH 5 produced no disturbance. The daily food and amino acid intake averaged 1,695 calories. The small amount of protein came from a processed vegetable soup, butter and cream, and tapioca. The remaining diet consisted of fruit juices, sucrose, lactose, and corn starch. There was no vomiting. Laboratory data did not change significantly.

Throughout period 3 the amino acids were given intravenously without reaction. The plasma nitrogen given, totalling 5.88 grams, and the red cell nitrogen, 19.32 grams, are not included in the nitrogen intake of period 3, Table III. The patient's general condition showed much improvement by this period. The caloric intake averaged 2,623, but on the last day he vomited a large amount of fluid and food, nitrogen content 1.17 grams. Before the first transfusion the total protein of the plasma was 3.8 grams per 100 cubic centimeters; after the second transfusion it was 4.8 grams per 100 cubic centimeter. There was no edema at any time. The albumin:globulin ratio was 1.5.

In period 4 the patient was tested again on voluntary feeding. He complained of fullness after moderate intakes on the first 2 days and vomited on the third day, 1.28 grams nitrogen including gastric washings from a Levine tube which was then inserted. Food intake was very poor on the third and fourth days and not accurately known. On the fifth day his abdomen was opened under general anesthesia and chronic intestinal obstruction was found due to chronic inflammation of lower jejunum and upper ileum beginning about 2 feet distal to the ligament of Treitz. A segment of ileum about 12 inches long was resected and a side-to-side anastomosis done. The specimen showed 3 greatly narrowed thick walled areas with intervening dilatations as much as 7.5 centimeters in diameter. The mucosa was ulcerated and microscopically there was a nonspecific acute and chronic inflammation. The picture was not thought to be entirely like that of regional enteritis. The patient withstood the operation well. A liter of normal saline was given under the skin. Sulfathiazole was placed in the wound and sodium sulfadiazine was given intravenously for 2 days postoperatively. The day before operation the plasma protein level was 5.5 grams per 100 cubic centimeters. The stool collection for this period was accidentally discarded without nitrogen analysis.

In period 5 amino acids 200 grams daily were given for the first 2 days and 100 grams thereafter. Sodium lactate chemically equivalent to the chloride content was given with the amino acids. The patient had an afebrile postoperative period except for a rise to 37.9 degrees C. on the day after operation. He took clear fluids moderately well for the first 3 days postoperatively and then increased to a diet similar to the preoperative one. The caloric intake averaged 1542 calories daily, being 2250 on the last day. On this fifth day he complained of feeling "queer" midway during the first injection of amino acids (50 gm. in 120 minutes) and again about 15 minutes after the second injection (50 gm. in 60 minutes). He could not describe the feeling except that there seemed to be a sense of fullness of the abdomen. The plasma protein concentration rose from 4.5 at the end of the second postoperative day to 5.4 grams per 100 cubic centimeter at the end of the fifth day after operation.

In the sixth period the amino acids were discontinued and diet was changed to include steak, milk, eggs, and other foods totalling 18.8 grams nitrogen and 3130 calories per day but was less than two-thirds consumed the first 2 days. General condition and appetite continued to improve. Total plasma proteins at the close of the period were 5.9 grams per 100 cubic centimeters.

The metabolic study was continued for 8 periods beyond those of Table III, with the same diet intake, with and without testosterone and has been reported elsewhere (3). Nitrogen retention was great and at the end of the 40 days the weight was 49.9 kilograms.

CASE 3. H.S. (SMH 203,122) was a white female, aged 53 years, with obstructive jaundice. At operation the gall bladder and common duct were distended with stones and white bile and a hard nodule was palpated in the head of the pancreas. After a cholecystogastrostomy the icterus subsided very slowly, the wound drainage was bile stained, and the patient's general condition and food intake were very poor. Thirty days later another exploration revealed that the common duct wound had broken down and the cholecystogastrostomy had closed. A choledochojejunostomy was performed, with the patient in and out of shock. Food and fluid intake after operation were very poor for 2 days. There was much vomiting. The patient's veins were poor for intravenous work. On the third postoperative day amino acid feeding was begun. At this time the plasma protein concentration was 4.8 grams per 100 cubic centimeters, plasma albumin 3.0 grams per 100 cubic centimeters, serum chlorides 100 milli-

TABLE IV.—HIGH PROTEIN FEEDING INFLUENCES RAPID HEALING OF CHRONIC WOUND

O. M., aged 8 years, unhealed burn, duration 1 year

Period 5 days	Clinical remarks	Nitrogen intake per period	Nitrogen output per period				Nitrogen balance* per period	Weight
			Urine Total	Urine urea-NH_3	Urine undetermined	Feces		
1	Pinch grafts	Grams 84	Grams 55.6	Per cent 87	Grams 7.0	Grams 4.1	Grams +24	Kilograms 19.2
2	Tonsillitis	94	59.0	86	8.3	10.0	+25	
3	Pinch grafts	80	51.6*	87	6.8	9.0	+15	
4		97	55.6*	87	7.4	4.8	+26	21.5
5		97	63.0*	81	11.6	7.1	+21	
6	Split grafts	50	39.4*	83	6.7	5.4*	0	
7		89	51.7*	86	7.2	6.4	+29	23.3
8		97	52.2*	85	8.0	10.7	+24	

*Incontinent—balance estimated.

equivalents per 100 cubic centimeters, icterus index 35.

In period 1 amino acids were given subcutaneously twice daily except for 2 intravenous injections. The caloric intake was poor as the patient tended to vomit when anything accumulated in the stomach, and the net intake may be estimated at not over 500 calories per day including amino acids. No nausea or vomiting or other reaction was observed in relation to the amino acid injections. The entire food intake consisted of orange juice and lemonade fortified with sugar, and on 1 occasion a little tomato juice. The vomitus nitrogen amounted to 1.15 grams. Three plasma and 1 whole blood transfusions were given and their nitrogen content (about 25 gm.) is not included in the intake of period 1. The patient had considerably improved in clinical condition and subjective appraisal of life by the end of the period. The plasma protein total was now (last day of period) 6.4 grams per 100 cubic centimeters and the plasma albumin 3.3 grams, the icterus index 16 and the serum chlorides 103 milliequivalents per 100 cubic centimeters.

In period 2 amino acids were given entirely subcutaneously and the patient, now more alert and co-operative, retained daily an estimated total of 1600 calories, after deducting for loss in vomitus. Vomitus nitrogen amounted to 1.51 grams. The effect of the plasma transfusions was not sustained and the level of plasma protein declined 24 hours later to 5.0 grams per 100 cubic centimeters (first day of period 2).

A liquid diet was given after period 2 and the patient slowly but steadily improved and left the hospital. She returned 10 months after the observations of Table III and died in the hospital. At autopsy carcinoma of head of pancreas was found.

The study in Table IV is presented in this report because of the importance of the therapeutic principles it emphasizes. Chiefly these are that a high protein intake may shorten illness and save lives, and second that the best source of a high protein intake is a diet of natural foods—useful and spectacular though parenteral feeding may be.

The patient in this case had been treated in two hospitals for an entire 12 months (See Case 4, Table IV). She had been treated competently in all respects except for control of diet. Good diets had probably been ordered but no measurement of actual intake had been made. The plasma protein level was not regarded as low but it was suggested by those in charge of the case after 1 month in the second hospital that parenteral feeding with amino acids might build up the patient enough for grafts to take and grow.

There was no barrier in the patient to normal eating, except lack of appetite for the routine diet. Therefore, *oral feeding*, not parenteral, *was indicated*. The diet prescribed on the metabolism division catered to the child's taste and *the intake was measured*.

Within 2 months from the beginning of Table IV virtually complete healing was accomplished of what had resisted all previous treatment during 10 months. We do not mean to imply that the very high level of protein feeding used in this case (5 to 6 gm. protein per kilo) was absolutely essential to its success. A somewhat lower intake might have succeeded, though probably less rapidly.

Voluntary uncontrolled intake was not sufficient.

Attention should be directed to the *plasma protein level*. The total plasma protein was nearly 6 grams per 100 cubic centimeters at the beginning of Table IV. Yet the body was unable to mobilize enough protein to produce tissue to anchor skin grafts. Evidently the body was thoroughly depleted of protein even though the circulating plasma protein level was at the lower edge of the "normal" range. After high protein feeding with much protein being produced and retained, the circulating plasma protein level was 7 grams per 100 cubic centimeters, or higher. Such an observation suggests that a plasma protein level of 6 grams per 100 cubic centimeters may correlate with a poorer state of health than higher levels within the normal range.

The nitrogen balance data in Table IV are only approximately accurate in that intake was calculated from standard diet tables rather than actual chemical determination and output was not always completely measured on account of incontinence. In addition, nitrogen loss from the wound surface was not continuously measured. There can be no doubt, however, that the balance was strongly positive in all periods except the 6th, and the rapid clinical improvement and weight gain eloquently confirm the value of the treatment.

CASE 4. O.M. (SMH 215,143) was a thin white girl of 8 years with an unhealed burn of her right thigh and leg. One year and 11 days before the beginning of the observations of Table IV, she sustained a burn, largely 3rd degree, from a fire started in bed by a faulty electric heating pad. Four days later she was taken to an adjacent hospital. Infection was treated with sulfonamides.

Three months after the burn pinch grafts were applied, unsuccessfully. They were tried again a month later, still unsuccessfully. Eight months after the burn the granulating area was considered suitable again but the patient went into shock under the anesthesia before the grafts could be taken and applied. Plasma applications were made locally and more sulfonamide therapy was given locally. Ten months after the burn the patient was transferred to this hospital.

On admission she was thin and pale and 70 per cent of the surface of her right lower extremity was a pink wet granulation tissue devoid of skin. There was a 15 degree contracture at the knee. The plasma proteins were 6.36 grams per 100 cubic centimeter by refractometer, and the other routine laboratory tests appeared normal. A high protein, high vitamin diet was ordered and as much assistance was given her with eating as could be spared on a busy pediatric division. She ate "fairly well."

During the first month she had an upper respiratory infection and some intermittent fever possibly related to wound infection. Measurement of the nitrogen loss from the granulating surface was done by determining the nitrogen content of the dressings with correction by deducting the small nitrogen content of equivalent unused dressings. The measured loss was 1.06 grams nitrogen per day. Five weeks after admission, large split thickness skin grafts were applied with thrombin technique by Dr. Forrest Young. They did not take.

The reason for the failure of the grafts was not apparent. Infection was controlled. The plasma protein level was above 6 grams per 100 cubic centimeter and although thin the patient was eating and did not appear emaciated. It was, however, considered desirable to improve the nutritional status and a request for amino acid injections was made. The patient was transferred to the metabolism division. Since the patient was co-operative and could eat normally it was decided to urge the complete consumption of a measured high protein diet. Foods were selected according to the tastes of the patient. The diet was accurately weighed and net consumption carefully measured. Vitamin supplements were continued exactly as during the preceding 2 months. These were ascorbic acid 50 milligrams, brewer's yeast tablets 1.5 grams and oleum percomorph 1.0 milliliter daily.

At the beginning of period 1 the patient weighed 19.18 kilograms including wet dressings. The plasma protein level was 5.90 grams per 100 cubic centimeters (by macro-Kjeldahl analysis); the plasma albumin 3.70 grams per 100 cubic centimeters. The plasma chlorides and carbon dioxide-combining power were normal. There was no evidence of dehydration. Seven days before the beginning of period 1 about 12 pinch grafts were applied.

The diet contained in grams, milk 800, whole egg 200, lean ham 100, frankfurt 100, lean ground beef 100, bacon 30, American cheese 50, frozen fresh peas 50, dried prunes 50, white bread 50, butter 30, sugar 30, cocoa 15. The diet is calculated to contain about 132 grams protein and 2360 calories, with roughly equal weights of protein, carbohydrate, and fat. For a patient of 19 kilograms it provides 6.9 grams protein and 124 calories per kilogram, as much as required by a newborn infant. The diet was not given in its entirety, as listed, during any complete 5 day period. The patient ate very well, and usually most of the day. Some modifications were made and on some days portions of the diet were not eaten. All of these were weighed back and deducted from the net intake. The net intake, for example, of period 2 was above 6 grams protein per kilogram. Urinary nitrogen outputs were determined in 24 hour periods, fecal nitrogen in 5 day periods.

In period 2 it was strikingly evident that the recent pinch grafts were taking. In addition, spreading of new epithelium could be seen about some old grafts which had previously been buried by granulation tissue. The food intake continued high despite the occurrence of acute tonsillitis with fever.

More pinch grafts were applied in period 3, and as these grew and the patient's weight and strength improved markedly in periods 4 and 5 it was decided to cover the whole area again with split thickness grafts. This was done at the beginning of period 6. The patient stood the procedure well but there was no food eaten the first day and reduced quantities for the rest of the period.

All the grafts took and healing proceeded well. The high diet intake was continued for 20 days beyond period 8, Table IV, but accurate measurements were not made. The entire lower extremity was covered by intact skin at this time except for one small bare area which healed during the next 4 weeks. The patient now weighed 24.3 kilograms.

During periods 3 to 8 the patient had occasional nocturnal enuresis. The amounts of nitrogen lost were estimated by reference to the output on adjacent days when complete collection was obtained, and the balances given in Table IV were corrected by these amounts. Slight vomiting of food occurred after the large feedings in periods 6 and 7 and this was deducted from the intake—2.1 grams nitrogen in period 6 and 2.8 grams in period 7. The plasma protein level rose from the initial 5.9 grams per 100 cubic centimeters to 7.10 grams by the end of period 4 and remained at this normal level. The plasma albumin level rose from 3.70 to 4.40 grams per 100 cubic centimeters.

After a month of physiotherapy the patient walked out of the hospital. She had slight residual contracture of the knee. There was some foot drop, possibly due to burn injury to the superficial peroneal nerve.

EVALUATION

Of what are amino acids capable? When is their use indicated? Are they toxic? Are they practical? Answers to all these questions are not completely given in the comments accompanying the observations presented but the trends of the answers are suggested.

Proper mixtures of amino acids *are capable of providing the protein nitrogen requirements of man and animals* over long periods of time. They may be given either by mouth, by vein, or by subcutaneous injection. Intraperitoneal injection has been successfully used in the dog (20). The importance of continuously adequate nutrition need not be discussed here. Either mixtures of crystalline amino acids or certain protein digests are capable of providing the protein share of it.

The formula for the perfect preparation of protein nitrogen is yet to be written. There are advantages and disadvantages to all substitutes for natural protein. Digests are of less known composition, more difficult of reduplication, more inflexible in composition, currently are less tolerable upon rapid injection than certain synthetic mixtures of amino acids. On the other hand they are inexpensive to produce. Amino acid mixtures contain the unnatural isomers of certain amino acids, but as discussed later no real toxicity has been demonstrated for these unnatural isomers. The question of better utilization of amino acid mixtures or digests favors the former, as judged by plasma protein production experiments in dogs (20). There appears to be little difference between amigen and mixture vuj intravenously in the brief test in Table I. By mouth, in the comparison of Table II, amigen is associated with a lower undetermined fraction of urinary nitrogen, but this test is clouded by the exacerbation of diarrhea (Case 1, Table II). Use of the mixture vuj in dogs (18) indicates a lower tolerance for it than the tolerance for some other mixtures (21). These latter and others should be tested in man.

Uses for amino acids other than the general nutritive one may be expected to appear. Individual amino acids or mixtures of individuals may be involved. The use of methionine in circumventing or alleviating toxic agents has been described in dogs (22, 13) and tested clinically (5, 14). It is a further stimulating suggestion that most of the effect of added protein intake in preventing negative nitrogen balance after injury (18) may be achieved equally well by added methionine (9), an observation not yet confirmed (27).

Indications for the use of amino acids for nutritional purposes exist only when natural protein cannot be effectively used. The study in Table IV demonstrates the importance of vigorous effort in the use of natural protein. Anyone who might order parenteral feeding in such a case because of its superficial ease or therapeutic impressiveness can recognize from such comparisons in Tables I and II that efficiency of utilization may be sacrificed somewhat. However, for the feeding of pa-

tients who cannot or should not be given protein by mouth, their value parenterally is great.

There are indications for their use *orally*. They appear to have marked value in the treatment of peptic ulcer from the interesting work of Co Tui, using amigen. Here their buffering capacity may be as important as their nutritive value. Used to fortify the diets of protein depleted individuals they should theoretically have considerable value. Such individuals must have reduced capacity to secrete the intestinal enzymes, which are proteins. Predigested protein should therefore be better handled. To illustrate this point an observation of Reifenstein and Albright is pertinent. A young man fed wholly by parenteral amigen and glucose for 26 days was given at the next meal a full diet of natural food by mouth. He accepted it and digested it without the slightest disturbance. A fasting individual, protein depleted, would usually not be capable of this but must start with cautious feeding gradually increased. The difference appears to lie in the reduced capacity of the depleted individual to produce gastrointestinal juices and enzymes.

No serious toxicity has yet been described with the use of proper amino acid mixtures or digests. Intolerance to the rapid injection of amino acid mixtures containing glutamic acid or much aspartic acid is manifested by vomiting in dogs (21, 16). The usual casein digests contain considerable glutamic acid. It is suggested in the observations of Table I of this paper that phenylalanine may be less tolerable than the other essential amino acids. Toxicity has been inferred for unnatural isomers but is not proved by the demonstration of interesting urinary metabolites related to their administration (1).

The use of amino acids will become increasingly practical. Further improvements are desirable in the palatability of oral preparations. Greater availability of the more tolerable intravenous preparations, such as proper mixtures of the crystalline amino acids or of digests free of glutamic acid and aspartic acid, should be provided. Complete parenteral feeding is not now limited by the nitrogen intake so much as by the lack of suitable means of providing a high caloric intake. Efforts to produce a satisfactory fat emulsion for intravenous administration have been long but are not yet successful (11).

SUMMARY

There are two sources of protein for meeting the needs of the body. One is that portion of body protein which can be mobilized for a particular need in time of emergency—called the reserve protein. The other is the main and ultimate source of protein, the exogenous intake, normally dietary.

Of the two general routes for supplying the exogenous protein needs in disease therapy, the oral route is shown to be preferable. The parenteral routes are shown to be valuable, even life-saving, when oral intake is impossible or inadvisable.

Mixtures properly prepared of the crystalline amino acids threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine, arginine, and glycine are adequate for the protein nitrogen needs and marked weight gain of patients over long periods of time. Given parenterally as the sole protein nitrogen intake these amino acids are adequate for nitrogen balance in human patients.

Histidine omission from a mixture of amino acids given intravenously to a patient with ulcerative colitis resulted in a negative nitrogen balance.

One amino acid mixture gave similar nitrogen retention and urinary nitrogen partition to that obtained with the protein hydrolysate amigen during a brief comparison. Neither was quite so well utilized parenterally as orally and neither was quite so well utilized orally as the better natural food proteins.

No toxicity to the unnatural isomers of 7 essential amino acids was demonstrated.

These crystalline amino acid mixtures are well tolerated subcutaneously as well as intravenously even in more than 12 per cent concentration in aqueous solution. It appears, moreover, that further improvements in tolerance can be made. Phenylalanine has been shown to be a limiting factor in tolerance.

Marked clinical improvement occurred in a patient with chronic ulcerative colitis fed

certain amino acid mixtures parenterally together with carbohydrate, fat, and accessories orally. No improvement occurred when the amino acids were also given orally.

The value of certain amino acid mixtures in the preoperative and postoperative nutrition of 2 patients was also demonstrated.

Plasma protein levels in the range commonly regarded as "low normal" may be found in patients showing virtually complete exhaustion of body protein reserves. A high protein intake actually measured and given to such a protein depleted patient with a chronically unhealed wound brought about complete healing after all other treatment had failed.

REFERENCES

1. ALBANESE, A. A. Bull. Johns Hopkins Hosp., 1944, 75: 175.
2. ALBANESE, A. A., HOLT, L. E., FRANKSTON, J. E., and IRBY, V. Bull. Johns Hopkins Hosp., 1944, 74: 251.
3. BASSETT, S. H. Josiah Macy Jr. Foundation Reports, June, 1943, ref. 4, p. 126.
4. BASSETT, S. H., WOODS, R. R., SHULL, F. W., and MADDEN, S. C. N. England J. M., 1944, 230: 106.
5. BEATTIE, J., and MARSHALL, J. Nature, 1944, 153: 525.
6. BROWNE, J. S. L. Josiah Macy Jr. Foundation Reports, February, 1944, ref. 6, p. 67.
7. BRUNSCHWIG, A., CLARK, D. E., and CORBIN, N. Ann. Surg., 1942, 155: 1091.
8. CLARK, D. E., and BRUNSCHWIG, A. Proc. Soc. Exp. Biol., N.Y., 1942, 49: 329.
9. CROFT, P. B., and PETERS, R. A. Lancet, Lond., 1945, 1: 266.
10. CUTHBERTSON, D. P. Lancet, Lond., 1942, 1: 433.
11. DUNHAM, L. J., and BRUNSCHWIG, A. Arch. Surg., 1944, 48: 395.
12. ELMAN, R., and WEINER, D. O. J. Am. M. Ass., 1939, 112: 796.
13. GOODELL, J. P. B., HANSON, P. C., and HAWKINS, W. B. J. Exp. M., 1944, 79: 625.
14. HIMSWORTH, H. P., and GLYNN, L. E. Lancet, Lond., 1944, 1: 457.
15. HOWARD, J. E., PARSON, W., STEIN, K. E., EISENBERG, H., and REIDT, V. Bull. Johns Hopkins Hosp., 1944, 75: 156.
16. MADDEN, S. C., ANDERSON, F. W., DONOVAN, J. C., and WHIPPLE, G. H. J. Exp. M., 1945, 82:77.
17. MADDEN, S. C., CARTER, J. C., KATTUS, A. A., JR., MILLER, L. L., and WHIPPLE, G. H. J. Exp. M., 1943, 77: 277.
18. MADDEN, S. C., and CLAY, W. A. J. Exp. M., 1945, 82: 65.
19. MADDEN, S. C., KATTUS, A. A., JR., CARTER, J. C., MILLER, L. L., and WHIPPLE, G. H. J. Exp. M., 1945, 82:181.
20. MADDEN, S. C., WOODS, R. R., SHULL, F. W., and WHIPPLE, G. H. J. Exp. M., 1944, 79: 607.
21. MADDEN, S. C., WOODS, R. R., SHULL, F. W. REMINGTON, J. H., and WHIPPLE, G. H. J. Exp. M., 1945, 81: 439.
22. MILLER, L. L., ROSS, J. F., and WHIPPLE, G. H. Am. J. M. Sc., 1940, 200: 739.
23. RATNER, S., SCHOENHEIMER, R., and RITTENBERG, D. J. Biol. Chem., 1940, 134: 653.
24. REIFENSTEIN, E. C., JR., and ALBRIGHT, F. Josiah Macy Jr. Foundation Reports, October, 1944, ref. 8, p. 168.
25. ROSE, W. C. Physiol. Rev., 1938, 18: 109.
26. ROSE, W. C., HAINES, W. J., and JOHNSON, J. E. J. Biol. Chem., 1943, 146: 683.
27. SCHENKER, V., and BROWNE, J. S. L. Josiah Macy, Jr. Foundation Reports, June, 1945, ref. 10, p. 303.
28. TUI, CO, WRIGHT, A. M., MULHOLLAND, J. H. GALVIN, T., BARCHAM, I., and GERST, G. R. Gastroenterology, 1945, 5:5.
29. VAN SLYKE, D. D., and KUGEL, V. H. J. Biol. Chem. 1933, 102: 489.

REPAIR OF LARGE ABDOMINAL DEFECTS BY PEDICLED FASCIAL FLAPS

OWEN H. WANGENSTEEN, M.D. F.A.C.S., Minneapolis, Minnesota

TWO PEDICLED FASCIAL FLAPS FOR CLOSURE OF LARGE DEFECT IN UPPER ABDOMEN

LARGE fascial defects in the upper abdomen, as a result of antecedent operations, are difficult of satisfactory closure by any method. A number of years ago (1932 and 1934), the present writer described the repair of recurrent and difficult hernias and other large defects of the abdominal wall employing the iliotibial tract of fascia lata pedicled on the tensor fascia femoris muscle as a graft. This method constitutes a very satisfactory means of dealing with large defects of the abdominal wall situated below the umbilicus. Even in patients with long femurs, the longest possible length of iliotibial tract of fascia is usually too short for the repair of defects immediately beneath the costal margin without tension. Furthermore, attempts directed at approximating the widely separated fascial edges in an incisional hernia of wide dimensions anywhere in the abdomen are probably ill advised. First, because sutures tied under tension invite necrosis of the approximated tissues and the recurrence of the hernia. Second, leaving the abdominal wall tight as a drum in the process of repairing a large ventral bulge may in itself invite disaster, owing to the baneful effects of increased abdominal pressure.

Necessity compels search for a satisfactory method of dealing with such hernias. In the latter part of 1944, when confronted with a very large hernia in a vertical incision extending from the ensiform cartilage to a few centimeters below the umbilicus, I hit upon the method to be described herein. Fortunately, however, the patient was thin and it was possible to approximate the wound edges of the defect without too great tension. A few months later, however, a patient presented himself with a large defect originating beneath the right costal margin and extending well beyond the midline. At operation the fascial defect measured 24 centimeters in length and 18 centimeters in width. No local sliding of tissue could possibly have succeeded in closing the defect. The antecedent story is as follows:

Mr. L. L., aged 63 years, University Hospital No. 728905, was admitted with acute intestinal obstruction, associated with large distention of the colon on June 21, 1943. "Transverse colostomy" was done a few hours after admission. The intraluminal pressure was 12 centimeters of water; 2000 cubic centimeters of gas was aspirated on closure of the skin. On June 30, 1943, primary resection was done for the obstructing carcinoma in the pelvic colon, which proved to be an adenocarcinoma on microscopic examination. The tumor was adherent to the left ureter, necessitating division and ligation of the ureter. A diverticulum of the bladder also was excised. Thirty (30) centimeters of colon was removed; the bowel and tumor weighed 440 grams. Colonic continuity was established by oblique end-to-end anastomosis. The patient was dismissed from hospital 20 days later, and returned for closure of the colostomy on July 28, 1943.

In August, 1944, the patient returned because of the presence of a large tumor in the abdominal wall near the umbilicus. About a year previous to the decompressive colostomy done here for acute obstruction, the patient had undergone repair of a large umbilical hernia elsewhere with excision of the umbilicus. On August 18, 1944, I operated upon the patient again for excision of the abdominal wall tumor, believed to be an implantation transfer of malignancy to the abdominal wall, during excision of the carcinoma of the pelvic colon.

A good portion of the abdominal wall had to be sacrificed and a loop of small intestine was also excised. The abdominal wall could not be closed satisfactorily owing to the large defect occasioned by excision of the abdominal wall tumor. On microscopic examination, the growth proved to be a desmoid tumor. The desmoid tumor weighed 375 grams and measured 8 by 7.5 by 6.5 centimeters.

A large hernia resulted (Fig. 1). The patient was operated upon for repair of this defect on March 6, 1945. The defect was very large, measuring 24 by 18 centimeters. The hernia was repaired by the method illustrated in Figure 2. Intimate adherence of a loop

From the Department of Surgery, University of Minnesota Hospitals, Minneapolis.

of small intestine to the lower margin of the hernial sac necessitated sacrifice of a loop of small intestine approximately 15 centimeters in length. Intestinal continuity was restored by oblique end-to-end anastomosis. Soon after the start of the operation, and frequently throughout the procedure, the patient's pulse was often very slow; on one occasion it was counted over a period of several minutes at 32 beats per minute. When the pulse was slow, the blood pressure also was usually low, frequently as low as 70 centimeters mercury. The cause of this phenomenon remained obscure. A cardiogram made directly after operation failed to indicate any evidence of coronary disease. This queer behavior of the pulse and blood pressure may have been due to the cyclopropane anesthesia which was employed in all the procedures. I am inclined to believe, however, that it was a "vagus" effect, occasioned by manipulation of the intestine—a circumstance which I have observed previously, particularly when the intestine is distended.

The patient did well and left the hospital on March 20, 1945, 11 days after operation. Subsequent examinations indicate that the abdominal wall is strong and firm with no suggestion of a defect or recurrent hernia. Recent photographs indicate that the functional result is excellent (Figs. 3 and 4). There is no evidence of recurrence of the desmoid tumor or of the cancer of the colon.

TECHNIQUE

In the instance herein recorded, a large flap of the fascia covering the entire right rectus muscle and the greater portion of the left rectus muscle also was delineated. The dissection was begun just below the most lateral extent of the hernial defect on the left, the incision extending vertically downward to the pubis. On the right side the fascial flap contained a good portion of the external oblique aponeurosis as well. The flap was mobilized from below upward, but not quite to the lower edge of the hernial defect. At the right extremity of the hernial defect, muscular fibers of the external oblique muscle were present in the mobilized flap. In the lower abdomen, the dissection was carried laterally to bare the spermatic cord in the inguinal canal.

This fascial flap, pedicled from its attachment at the inferior margin of the hernial defect, was quite adequate to cover the hernial opening. A large portion of the patient's small intestine had been contained in the hernial sac. In freeing the adherent loops of bowel, the peritoneal surface of one segment of jejunum was traumatized enough to suggest the necessity for resection of the segment, followed by an oblique end to end anastomosis. The fascial flap was sutured in place with interrupted sutures of fine silk (No. 000).

a b

c

Fig. 1. Photograph of patient, Mr. L. L., University Hospital No. 728905, before operation. a, b and c, Views of hernia in upper abdomen from various directions.

On completion of this procedure, the iliotibial tract of fascia lata pedicled on the tensor fascia femoris muscle was mobilized from the anterolateral aspect of the right thigh as shown in Figure 2. This technique has been described in detail elsewhere (2). A fairly large subcutaneous tunnel was established

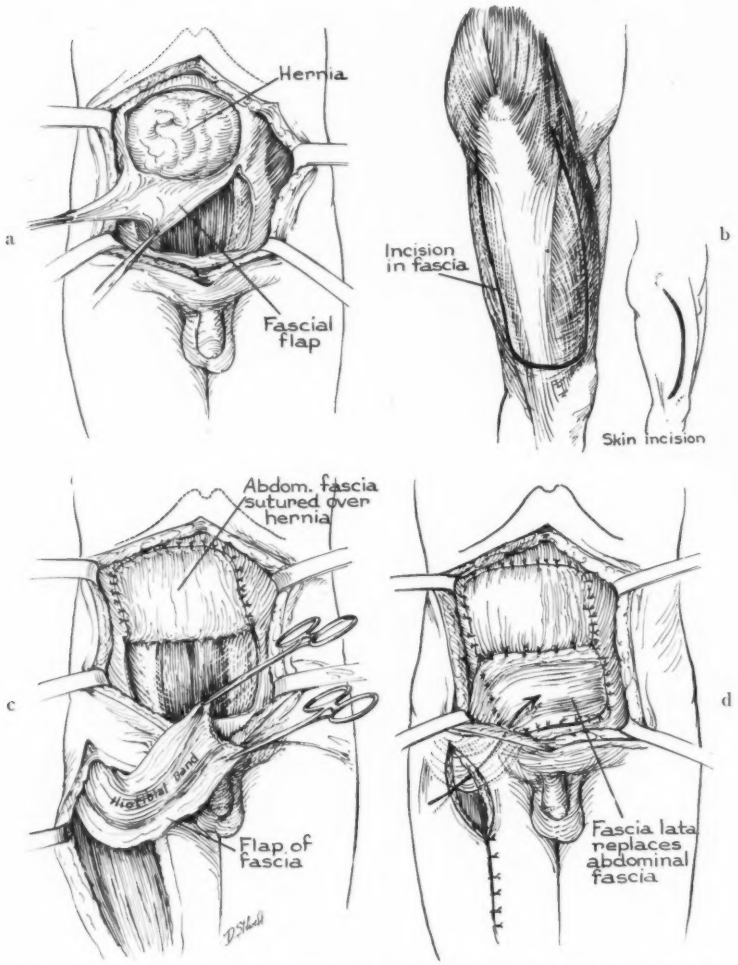


Fig. 2. Schematic drawings indicate the steps in the operative repair of the hernia shown in Figure 1. a, The defect immediately below the right costal margin, measuring 18 by 24 centimeters. A pedicled musculofascial flap is swung up from the lower abdomen to fill in the upper abdominal defect. The flap consisted of the entire anterior rectus sheath beneath the umbilicus, together with portions of the external oblique aponeurosis and fibers of the right external oblique muscle. b, The iliotibial tract and its lateral extensions of fascia lata demarcated as a flap. c, The fascial flap from the lower abdomen is swung into the abdominal defect. The pedicled flap from the thigh is ready to be brought over Poupart's ligament into the abdominal wound. d, Both flaps have been sutured in place.

over Poupart's ligament to permit drawing the fascial flap into the abdominal wound.

Prior to operation, it had been ascertained that the distance from the greater trochanter to the upper margin of the hernial defect was 36 centimeters. The greatest possible mobilizable length of iliotibial tract of fascia below the great trochanter was only 31 centimeters. Obviously the pedicled iliotibial tract could not be made to reach to the upper margin of

a b

Fig. 3.

a b

Fig. 4.

Fig. 3. Photographs made while the patient was still in hospital. a, The abdominal incision. b, The thigh incision.

Fig. 4. Photographs made 5 months after operation. a, The abdominal wall is strong; there is no evidence of a fascial defect or hernia. b, The thigh incision.

the hernial defect. It did suffice nicely, however, to cover the entire fascial defect in the lower abdomen created by swinging the first pedicled fascial flap.

REPLACEMENT OF INFRAUMBILICAL MUSCULOTENDINOUS PORTION OF THE ABDOMINAL WALL BY A SINGLE PEDICLED FASCIAL FLAP

The earlier presentation concerned itself primarily with the management of recurrent and difficult inguinal and femoral hernias (1934), by means of a pedicled fascial flap from the thigh. It is desired to record herewith the instance of a boy of 15 from whose lower abdomen a large desmoid tumor weighing 1500 grams was removed. In the removal of the tumor it became necessary to excise the greater portion of the musculotendinous structure of the infraumbilical portion of the abdominal wall. This large defect was closed easily and satisfactorily by swinging up the iliotibial tract of fascia lata which was pedicled on the tensor fascia femoris muscle, and was re-enforced by lateral extensions of the fascia lata.

E. B., University Hospital No. 686592, admitted to the University Hospital on October 23, 1939. Preoperative diagnosis: large abdominal tumor.

The patient, aged 15 years, gives a story of operation for acute suppurative appendicitis about 3 years previously; the three old scars on the abdominal wall, shown in the photograph (Fig. 5) indicate the sites of drainage at the time of appendectomy. He said that his abdomen enlarged gradually, but his father was not aware of it until just before admission, when he took his son to a local physician, who referred him here for operation. The tumor appeared to be in the abdominal wall. On rectal examination the tumor mass could be distinctly felt. A cystogram was made which showed a definite indentation of the bladder on the anterior abdominal wall, the bladder being pushed distinctly posteriorly. It was obvious that this would necessitate an enormous operative procedure to excise it; yet, in the light of previous experience with large defects in the lower abdomen, it did seem worth while to undertake excision of the tumor. Closure of the defect, it was believed, could be effected by the use of a fascial flap from one or both legs.

Operation was done on October 25, 1939 under intratracheal cyclopropane anesthesia. A vertical skin excision was made in the midline, extending from the umbilicus to the pubis, also a vertical incision on the lateral aspect of the thigh from just beneath the anterior superior spine to above the knee.

At operation there was found an enormous tumor which filled the entire pelvis, pushing the bladder posteriorly. There was an indentation on the tumor from pressure on the bladder. The tumor arose apparently from the rectus fascia in the lower abdomen and from the pubis. The removed tumor weighed 1500 grams.

TECHNIQUE

Through the aforementioned vertical incision, the tumor was gradually exposed. It was found to lie on the parietal peritoneum. The only site at which the abdominal cavity was opened was at the umbilicus. A slip of gut came up into the wound where the gut

a b

Fig. 5.

Fig. 5. Preoperative photograph of D. B., aged 15, University Hospital No. 686592. a and b, The large protuberance caused by the desmoid tumor of the abdominal wall. c, Indicates the posterior displacement of the bladder caused by the tumor. d, The tumor.

Fig. 5c.

was apparently attached to the umbilicus. The infraumbilical portion of the rectus muscles, including the anterior and posterior sheaths of both recti, the external oblique aponeurosis as well as the internal oblique, except for the musculotendinous portion of the abdominal wall lateral to the vas deferens and spermatic cord on each side, was sacrificed. The abdominal wall was undercut above the umbilicus, and a bit of the rectus muscles and sheaths extending above the umbilicus had to be excised. The resultant defect constituted a large area extending from the pubis below to about an inch above the umbilicus superiorly. The only portion of the lower abdominal wall remaining intact lay lateral to the spermatic cord on either side.

At this juncture a large flap of fascia including the iliotibial tract of fascia in the middle, and the extensions of the fascia lata covering the sartorius medially and the biceps femoris laterally, pedicled on the tensor fascia femoris muscle, was brought up beneath Poupart's ligament and sutured into the defect. As the

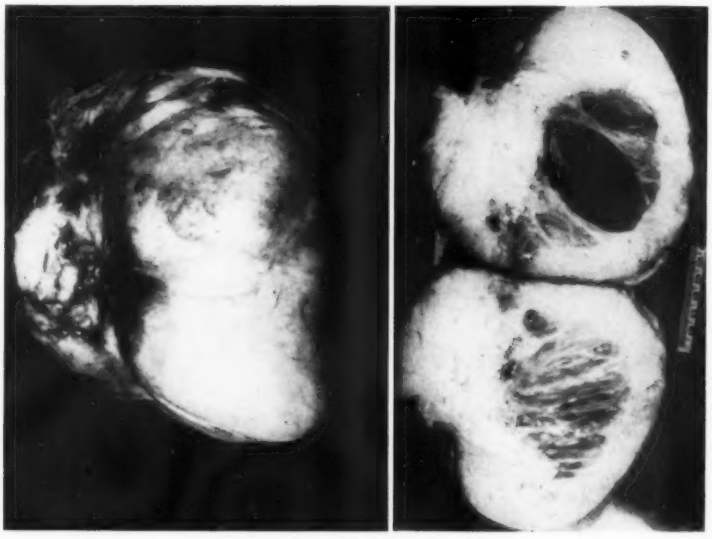


Fig. 5d.

operation was begun, it was thought that fascia from both thighs might be necessary. The generous unilateral fascial flap, however, proved quite adequate to close the defect. The musculotendinous defect into which the fascial flap was swung was 15 centimeters long and 13 centimeters wide. Because of the large persisting space overlying the bladder, occasioned by the removal of the tumor, it was thought well to leave a small drain in the prevesical space. The patient stood this prolonged operative procedure well, and left the table in good condition. No attempt was made to close the fascial defect in the thigh, the skin edges merely being coaptated with fine silk sutures. He was dismissed from hospital on November 29, 1939.

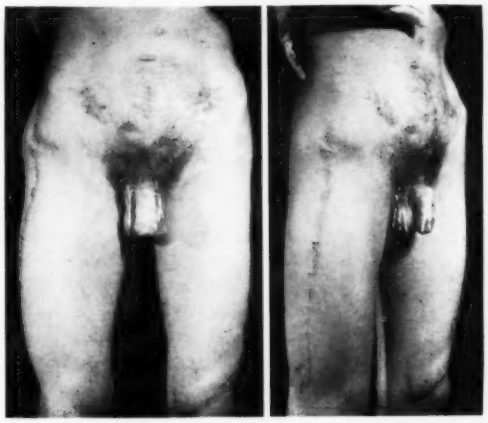
The pathological diagnosis (Dr. Robert Hebbel) follows:

The specimen consists of a sharply demarcated, somewhat lobulated mass measuring 14 by 15 by 12 centimeters. There are some attached portions of fascia and skeletal muscle. On section the tumor is fibrous and moderately firm. Centrally there is a large cystic area 7.5 centimeters in diameter which is filled with slightly mucoid fluid. The mass weighs 1500 grams.

Microscopic examination shows that for the most part cells are small and separated by an abundance of intercellular material. In a few areas, and particularly in a section of a fragment removed separately from just above the penis, the cells are more plump and present a greater amount of cytoplasm.

Conclusion: Fibrosarcoma, grade I, or desmoid tumor of the abdominal wall.

This boy, now 21 years of age, has been observed periodically in the outpatient clinic since the time of his operation in October, 1939. The abdominal wall is strong; there is no evidence of recurrence of the tumor, and there is no hernia. He is able to do heavy work, but was rejected for military service because of the history of the abdominal wall tumor. Shortly after the initial operation, my colleague Dr. Arnold Kremen, now on military leave, examined the literature of desmoid tumors. He told me that this tumor, weighing 1500 grams, was the largest desmoid tumor removed surgically on record since 1900.



a b

Fig. 6. A photograph made in June, 1945, more than 5 years after the operation. The abdominal wall is strong and there is no defect in the fascia, nor evidence of hernia. a, The abdomen. b, The incision in the thigh.

SUMMARY

A method is described for increasing the range of utility of the iliotibial tract of fascia, pedicled on the tensor fascia femoris muscle in the repair of abdominal hernias. By employing the pedicled iliotibial tract as a replacement for a pedicled fascial flap swung up from the lower to the upper abdomen, any hernia of the abdominal wall becomes amenable to treatment by this method. Heretofore, incisional hernias with large defects in the upper abdomen have been difficult problems to resolve by any of the available methods. The procedure herein described gives promise of constituting a means of dealing satisfactorily with large defects of the upper abdominal wall. The method possesses the advantage over free fascial grafts of insuring satisfactory wound healing.

The instance of a patient having a defect 24 centimeters long and 18 centimeters in width in the upper abdomen, following excision of a large desmoid tumor of the abdominal wall is reported. A good firm abdominal wall resulted. A nonirritative, nonabsorbable suture such as fine silk is the suture material of choice for anchoring the pedicled grafts.

An instance is cited also in which the iliotibial tract of fascia pedicled upon the tensor fascia femoris muscle was employed to replace the larger part of the musculofascial portion of the abdominal wall below the umbilicus attending excision of a large desmoid tumor

weighing 1500 grams. The defect was 15 centimeters in length and 13 centimeters in width. A single pedicled graft of the iliotibial tract supplemented by its lateral extensions of fascia lata sufficed to fill the defect.

Removal of such large fascial flaps from the thigh does not impair its function and is not followed by untoward effects.

ADDENDUM—

Since this paper was submitted for publication, 3 additional patients have been operated upon for the repair of large abdominal defects. In the first, a patient with an unusually large incisional hernia, the plan of operation described herein was employed. Each of the other 2 patients presented a large carcinomatous mass in the abdominal wall following a Mikulicz exteriorization operation for cancer of the pelvic colon. The case records follow.

CASE 1. Mrs. A. E., aged 66 years, University Hospital No. 601240, was admitted on September 30, 1945, for repair of a large incisional hernia following drainage of the gall bladder (long vertical right rectus incision), performed elsewhere several years previously. An unsuccessful attempt had been made before admission here to repair the hernia. The defect was enormous and extended from the pelvis to the costal margin. In extent, the defect measured 26 by 21 centimeters. The scheme described in this paper was employed to close the defect. Fascial flaps from the lower abdomen constituted by the anterior rectus fascia and its lateral extensions were delineated from both sides of the long vertical defect. The upper and most lateral wing of each of these pedicled fascial flaps was swung upward to close the upper portion of the herniæ defect. The longest and widest possible pedicled fascial flap was swung up from the right thigh, pedicled on the tensor fascia femoris muscle, employing the entire iliotibial tract of fascia. A satisfactory closure of the large defect was obtained. The abdominal wound healed kindly and the abdominal wall appears strong with no suggestion of a persistent defect. Owing to the curved nature of the incision on the thigh, a small slough occurred at the convex portion of the skin flap which prolonged the hospital stay. The final result seems to be very satisfactory.

CASE 2. Mrs. J. K., aged 66 years, University Hospital No. 757515, was admitted to the University Hospital on August 29, 1945, for a recurrent carcinoma of the abdominal wall and sigmoid colon following an exteriorization operation performed elsewhere 3 years previously. Excision *en masse* of abdominal wall and colic tumor with primary closed anastomosis. A mucocele of the appendix was excised also. A large fascial flap pedicled on the tensor fascia femoris muscle from the left thigh sufficed to fill the large abdominal wall defect. The patient was dismissed from hospital 8 days after operation. The abdominal wall is strong.

CASE 3. Mr. G. S., aged 64 years, University Hospital No. 760142, was admitted on November 14, 1945, had a large fungating cauliflower lesion in the abdominal wall. Two earlier Mikulicz exteriorization procedures had been done elsewhere for a carcinoma of the lower pelvic colon, the first 2 years prior to admission here. At operation, November 19, 1945, the major part of the infraumbilical portion of the abdominal wall was excised including the skin. There was a single large metastasis in the liver which was said to have been present already at the time of the first exteriorization operation done 2 years previously. The tumor involved the rectosigmoid area and was intimately adherent to the bladder and several coils of small intestine. There was a separate fairly large carcinoma in the midtransverse colon. The left ureter was sacrificed. The tumor of the abdominal wall was excised *en masse* with the colon and a primary closed anastomosis was effected between the proximal third of the transverse colon and the rectum 11 centimeters from the anus. The resultant abdominal defect involved all the structures of the abdominal wall including skin, fascia, muscle and peritoneum; the defect was 20 centimeters from above downward, and 16 centimeters across in a horizontal direction. A long fascial flap was swung up from the left thigh which replaced satisfactorily the peritoneofascial defect. The skin was closed by a sliding maneuver. This 10 hour operation was withstood nicely by the patient. Owing to some tension, a slough occurred in one of the skin flaps necessitating a secondary skin graft. The patient otherwise made a satisfactory convalescence and the abdominal wall is strong. At present, the patient is at home awaiting re-entry for excision of the hepatic metastasis.

REFERENCES

1. WANGENSTEEN, O. H. Minnesota M., 1932, 15: 439.
2. Idem. Surg. Gyn. Obst., 1934, 59: 766–780.

CHEMOTHERAPY AND CONTROL OF INFECTION AMONG VICTIMS OF THE COCOANUT GROVE DISASTER

MAXWELL FINLAND, M.D., CHARLES S. DAVIDSON, M.D., and
STANLEY S. LEVENSON, M.D., Boston, Massachusetts

At the time of the Cocoanut Grove disaster, opinions concerning the efficacy of various forms of sulfonamide therapy in wounds and burns were still divided. Lyons (3) had reviewed the literature dealing with the rationale of local sulfonamide therapy and also the somewhat meager clinical reports then available on its prophylactic value. He observed that "the rather enthusiastic clinical adoption of local sulfonamide therapy had failed to provide factual data for analysis of the extent to which such treatment had prevented the growth of bacteria in wounds."

Such data were being accumulated at that time by the Contaminated Wound and Burn Projects sponsored by the Subcommittee on Surgical Infection of the National Research Council. The results of these carefully controlled observations were already providing evidence which served to temper considerably the enthusiastic reports brought back by some of those who had an opportunity to observe the casualties at Pearl Harbor.

Based on the evidence which was available at that time and which was subsequently confirmed and greatly amplified in Meleney's report (5), the "Burns Project," as set up at the Boston City Hospital at the time of the Cocoanut Grove fire, did not include the local use of sulfonamides. There were only 2 cases among the Cocoanut Grove victims at this hospital in which sulfanilamide powder was applied locally on some occasions and 2 others in which sulfathiazole ointment was applied to some of the burned areas about the face. This therapy, however, played only a minor rôle in the management of these cases.

The systemic use of sulfonamides in the present cases was undertaken from two separate, though similar, considerations. First, with respect to the surface burns it was thought that chemotherapy might be useful in limiting infection to the burned areas, and that cellulitis and septicemia might thereby be prevented. Secondly, since respiratory tract involvement constituted such an important part of the injuries in these cases, the use of sulfonamides was considered to be the best available means of preventing or minimizing pulmonary infections which were expected to complicate these injuries. These indications seemed reasonable on the basis of the known clinical experience although there was very little in the way of conclusive evidence from published reports that the drugs would serve those purposes.

The administration of sulfonamides in many of the present cases involved considerable difficulties. Because of the wide differences in the general condition of the patients, in the extent of their surface burns and respiratory injuries and in other incidental complications, the treatment had to be individualized and controlled with great care. The major problems arose chiefly from 3 sources, namely: (1) shock and its effect on the circulation and on renal function, (2) impairment of renal function associated with hemoglobinuria, and (3) difficulties in maintaining proper water and electrolyte balance, particularly in view of the use of large amounts of plasma and the tendency on the part of some of the surgeons to avoid the administration of additional fluids. All 3 of these factors were thus focused on the one point of avoiding the most frequent of the serious complications of sulfonamide therapy, namely, those involving the urinary tract.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Burn Assignment to the Surgical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

The work described in this paper was done, in part, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

The present report comprises an analysis of the sulfonamide therapy as actually used in the cases admitted to the Boston City Hospital from the Cocoanut Grove fire. An attempt will be made to evaluate the results of this therapy as far as that can be done from the data available. The bacteriological findings are summarized for some of the cases in which significant infection occurred in the burned areas and in the respiratory tract. The relevant findings with respect to fluid and drug administration in illustrative cases and groups of cases will be summarized.

ANALYSIS OF THE SULFONAMIDE THERAPY USED

As already intimated, neither the local nor the systemic use of sulfonamides formed a part of the program of the routine management of burns in this hospital at the time of the disaster. During the first few hours after the fire, little attention was therefore paid to the problem of chemotherapy in the present cases and only an occasional patient received it orally or as part of the parenteral fluid therapy given at that time.

Selection of cases for sulfonamide therapy. During the surveys of all the patients which were made by the authors on the morning and evening after the fire and at regular intervals thereafter particular attention was paid to the problem of sulfonamide therapy. Details of the therapy prescribed depended on the state of hydration, the urine output, the ability of the patient to take medication orally and the results of blood studies. In many instances it was considered inadvisable to start therapy during the first day or two because of the low or absent urinary output, because of nitrogen retention, hemoglobinuria or for other reasons. In other patients with minor burns, treatment was not given at first but was started later, usually because of the respiratory tract complications.

A total of 76 patients received sulfonamide therapy. In Table I there is given an analysis of these cases with respect to the time when the treatment was begun, its duration, and the total amount of drug used. The cases are arranged according to the severity of respiratory tract involvement. Sulfonamides were not used in 24 of the fatal cases and in 31 of the survivors. The former included most of the patients who had the most extensive surface burns and were in shock at the time of arrival or shortly thereafter and also those with the severest respiratory tract damage who had symptoms of respiratory obstruction soon after they arrived. All of these patients died during the first 2 days and 15 of them died within the first 24 hours. Among the survivors who were not given sulfonamide drugs were 19 patients who were discharged or transferred to other hospitals during the first 18 hours, 4 others with minimal involvement who were discharged within 36 hours and 2 who were kept in the hospital for injuries other than burns. The remaining 6 patients had burns involving 5 per cent or less of the surface area, which were not severe and were associated with minimal, if any, respiratory complications. Slight and transient fever occurred in 3 of the latter patients and that constituted the only evidence of possible infection among the patients who did not receive sulfonamide drugs.

Time of beginning treatment. Treatment was begun within the first 24 hours in 20 of the cases, during the second day in 40 cases, and later in the remaining 16. Half of the cases of each of the first 2 groups had severe respiratory symptoms and the others had either moderate respiratory damage or fairly extensive burns. Only 3 of the 16 patients in whom treatment was begun on the third day or later had severe respiratory tract involvement. Two of them had no surface burns while the third had burns involving almost two-thirds of the body surface and died on the day after the drug was started. Among those with mild or moderate respiratory involvement in whom treatment was delayed, 3 had burns of 20 per cent or more of their body surface. Four had burns of 6 to 8 per cent and the rest had only minor burns. In only 1 of these patients (Case 59) did it seem likely that infection of the wound contributed materially to delay in healing or to the prolonged stay of the patient in the hospital. The delay in starting treatment was usually due to the factors already outlined, but chiefly to the fact that the patients had a poor urinary output.

Choice of drug. Sulfadiazine or its sodium salt was used more or less routinely and this drug was given to all but 5 of the 76 patients. Sulfapyrazine was used in 2 cases and sulfathiazole in 14 but in only 1 of the former and in 4 of the latter were these drugs used alone. In the remaining cases the sulfapyrazine or sulfathiazole was given after sulfadiazine either because the patient had untoward reactions attributable to sulfadiazine or as the supply of that drug was temporarily exhausted.

Route. It was considered desirable to use the oral route for administration of the sulfonamides as far as possible, this method offering the least likelihood of producing urinary tract complications. The intravenous route was used for the initial dose in some of the cases with the severest burns. In almost all such cases fluids other than plasma or blood were being given by this route and the patients were fairly well hydrated. All of the intravenous drug was given as sodium sulfadiazine dissolved in physiological saline in concentrations of 0.5 per cent or less of the drug. As far as could be ascertained, no renal complications occurred that could be attributed to the parenteral chemotherapy. An increase in the nonprotein nitrogen occurred in 2 fatal cases, but in both of them hemoglobinuria, oliguria, and some elevation of the nonprotein nitrogen were already present before the sulfonamide treatment was started.

Dosage. The initial dose of sulfadiazine which is customarily given to adults in this hospital is 4 grams orally or 5 grams of the sodium salt when given parenterally. In the present cases since the drugs were being used chiefly for prophylaxis and also because of the greater possibility of kidney injury and of difficulties of maintaining fluid and electrolyte balance, smaller initial doses were given in many of the cases. In 8 of the patients in whom treatment was begun by an intravenous injection, the initial dose was 2 to 3 grams and about one-half of those who received oral therapy were given 2 grams for the first dose. The latter was usually repeated after 4 hours. The maintenance dose was that which is customarily used, namely, 1 gram every 4 hours, but modifications were made from time to time as indicated by clinical and laboratory findings in the individual cases. In a few instances the parenteral injections were repeated once after 8 to 12 hours but only 1 patient received 3 and 1 other received 4 intravenous injections. All the parenteral injections given after the first one consisted of 2.5 grams of the drug.

Alkalis. The use of alkalis was limited chiefly to the patients with extensive burns. They were first given during the early survey of the patients because of the finding of some cases with hemoglobinuria among those who were severely burned. All of these patients in whom hemoglobinuria was detected and most of the others who had extensive burns were given alkalis at that time. They were administered in the form of sodium bicarbonate orally, when possible or in the form of ⅙ molar sodium lactate intravenously as a supplement to other parenteral fluids. The alkali therapy was intended as a preventive against possible renal complications. These were anticipated more because of the hemoglobinuria than from the chemotherapy although the latter consideration also entered into the decision to use the alkalis.

It must be stated, however, that the alkalis were not given without some hesitation. The possibility of water retention resulting from the sodium administration[1] and the consequent aggravation of the edema and exudation from the wounds or the development of pulmonary edema were considered. The finding of highly acid urine in the cases of hemoglobinuria was the deciding factor. An attempt was made wherever possible to adjust the dose so as to give a neutral or slightly alkaline urine. Usually 1 or 2 grams of sodium bicarbonate was given with each dose of sulfonamide. In most instances the alkalis were discontinued after the patient was able to take adequate amounts of fluid and to maintain a good urine output but it was stopped earlier if dependent edema developed outside of the burned areas or if the urine output continued to be small.

Duration of chemotherapy (*Table I*). Treatment with sulfonamides was maintained for an average of 11 days and a second course of

[1] Since the plasma used was derived from citrated blood these patients had already received considerable amounts of sodium from this source.

TABLE I.—ANALYSIS OF CHEMOTHERAPY AS USED IN THE CASES ADMITTED TO THE BOSTON CITY HOSPITAL FROM THE COCOANUT GROVE FIRE

Grade of respiratory involvement	None	Mild moderate	Severe	All cases
Number of patients who received sulfonamides	6^{1}	37^{2}	33^{12}	76^{15}
Sulfonamide therapy begun First day	1	9^{1}	10^{5}	20^{6}
Second day	4^{1}	16^{1}	20^{8}	40^{8}
Third day or later	1	12	3^{1}	16^{1}
Duration of sulfonamide therapy Less than 1 day	0	0	4^{4}	4^{4}
1–4 days	0	8	5^{8}	13^{8}
5–7	0	9	4	13
8–14 days	4	13	10^{1}	27^{1}
15 days or longer	2^{1}	7^{2}	10	19^{3}
Average number of days	17^{41}	10^{18}	11^{2}	11^{8}
Number who received drug parenterally	0	2^{2}	15^{10}	17^{12}
Average parenteral dose (grams)	—	4^{4}	6^{8}	5^{8}
Total dose (grams) Less than 10	0	1	4^{4}	5^{4}
10–24	0	8	6^{8}	14^{8}
25-49	0	10	6^{2}	16^{2}
50–99	5	14^{1}	11	30^{1}
100 or more	1^{1}	4^{1}	6	11^{2}
Average dose	97^{246}	56^{34}	58^{18}	60^{42}

The figures for the fatal cases are given in the superscripts.

TABLE II.—TOXIC EFFECTS FROM SULFONAMIDE DRUGS OBSERVED AMONG 76 CASES ADMITTED TO THE BOSTON CITY HOSPITAL FROM THE COCOANUT GROVE FIRE

Toxic manifestation	No. of cases
Fever without rash	4
Rash and fever	3
Leucopenia (4000 or less)	2
Hematuria (microscopic)	5*
Renal colic	1
Nitrogen retention	3†
Nausea and vomiting	2‡
Total number of patients	17

*Includes 1 with drug fever and 1 with renal colic.
†All had hemoglobinuria before sulfonamide therapy.
‡Includes 1 case with a rash.

therapy was given before and during skin grafts in a few cases and in some others because of recurrent fever. The cases in which the drug was used for 4 days or less included 9 in which death intervened and 8 in which the burns were either absent or of minor extent and severity and the respiratory damage was relatively mild. On the other hand, those in which treatment was continued for more than 2 weeks included most of the patients who had either extensive and severe burns or severe respiratory damage or both.

Total dose. The amount of drug used in each case was, of course dependent on the time over which it was given. The average total dose per patient was 60 grams which was only slightly less than 6 grams per day. This reflected the fact that, in general, full doses were maintained throughout the course of treatment. In a few instances, however, the daily dose was reduced temporarily because of retention of water, nitrogen, or drug.

Blood levels. Chemical determinations of sulfonamide levels in the blood were done frequently in some cases and irregularly in others. They were carried out frequently in patients in whom difficulties were encountered in the administration of fluids and also in those having abnormal urinary findings or high blood nonprotein nitrogen levels. Some idea of the drug levels found in the blood may be had from Figure 1 which shows the concentrations of free drug observed during the first 3 weeks. For the most part, as will appear later from the data of individual cases, there was a fairly constant and small amount of acetylated drug in the blood, about 1 milligram per 100 cubic centimeters in the majority of cases. The level of the free drug in the blood was most often between 4 and 8 milligrams per 100 milliliters. High levels were encountered more frequently during the first few days and low levels were more frequent after the first week. On the whole these low and irregular values reflect the difficulties in controlling the various aspects of chemotherapy in many of the patients, particularly those who were severely ill. This aspect, too, will appear from the charts of individual cases.

Toxic effects (Table II). An estimation of the frequency with which toxic effects were observed in the present group is necessarily inadequate. Some of the untoward manifestations were undoubtedly masked or went unobserved for one reason or another. In addition, it was difficult to determine whether or not certain manifestations were attributable

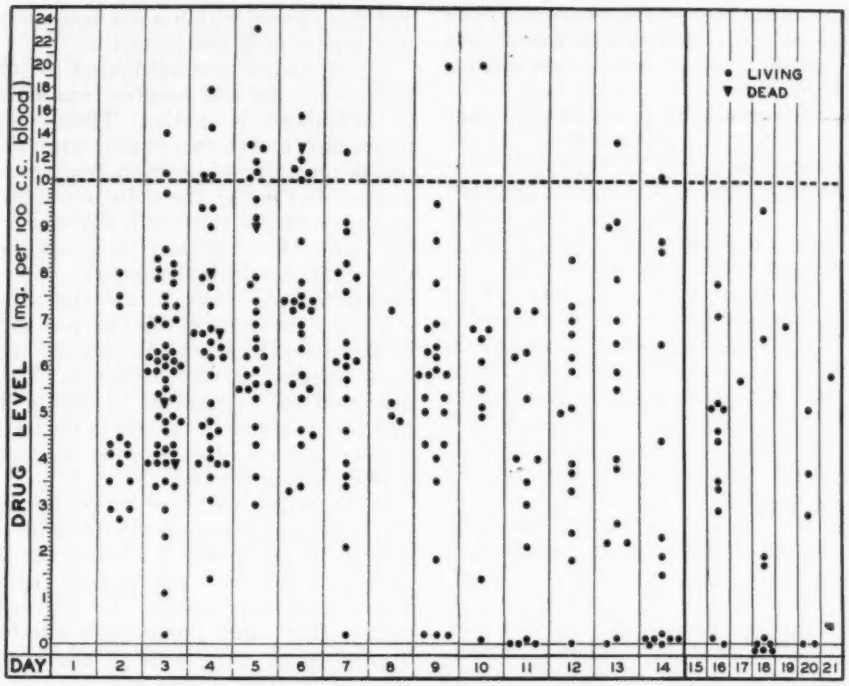


Fig. 1. Concentrations of free sulfadiazine in blood in Cocoanut Grove cases.

to the toxicity of the drug. Thus, there were 3 cases in which blood nonprotein nitrogen levels rose early in the course of therapy, but in each case hemoglobinuria, oliguria and abnormally high levels of nonprotein nitrogen were noted before the drug was first given.

There were 7 cases in which fever could be attributed definitely to drug toxicity. In 3 instances this fever was associated with a scarlatiniform or morbilliform rash (with episcleritis in one of them) which appeared on the fifth day in one case, on the seventh day in another and on the eighth day of the second course of treatment in the third case. In the latter, the same drug (sulfadiazine) had been given for 23 days during the first course and an interval of 3 weeks had elapsed before the second course was started. In each of these 3 cases the rash subsided when the sulfadiazine was stopped although sulfathiazole or sulfapyrazine was used to continue the treatment without interruption. Drug fever unaccompanied by a rash began on the 10th, 11th, 12th and 20th days, respectively, of sulfadiazine therapy. In each of the 4 cases the fever subsided within a day after the sulfadiazine was discontinued and in one of them sulfapyrazine was used to maintain chemotherapy without interruption. In one other patient a second course of sulfadiazine was given after an interval of 10 days and full doses were given for 5 days without a recurrence of the fever.

Urinary tract complications were observed in 5 cases in addition to the 3 with the nitrogen retention which have already been mentioned. Microscopic hematuria was the only manifestation of this complication in 3 cases. It was observed on the 7th and 9th day and was not accompanied by crystalluria. In the fourth case gross hematuria with dysuria occurred on the third day and cleared rapidly when the fluid intake and output were increased. In the fifth case there was renal colic accompanied by microscopic hematuria on the fourth day

TABLE III.—ANALYSIS OF THE OCCURRENCE OF FEVER IN CASES ADMITTED TO THE BOSTON CITY HOSPITAL FROM THE COCOANUT GROVE FIRE

Analysis of fever	Sulfonamide therapy				Total
	Given		Not given		
	Recovered	Died	Recovered	Died	
A. Onset of fever*:					
First day	40	11	3	10	64
Second day	18	2	—	1	21
Third day	—	1	—	—	1
Fourth day	1	—	—	—	1
Fifth day	1	—	2	—	3
Sixth day	—	1	—	—	1
No fever	1	—	8	1	10
Total	61	15	13	12	101
B. Duration of fever*:					
None	1	—	8	1	10
1 day or less	16	2	—	10	28
2 days	8	4	4	1	17
3 days	6	—	—	—	6
4 days	6	3	1	—	10
5–7 days	5	3	—	—	8
8–14 days	13	1	—	—	14
15 or more days	6	2	—	—	8
Total	61	15	13	12	101
C. Maximum temperature					
First 48 hours					
100–101°	30	6	3	3	42
102–103°	26	6	—	1	33
104° or higher	1	2	—	5	8
Total cases with fever	57	14	3	9	83
Total cases observed	61	15	13	12	101
Third and fourth days					
101–101°	17	5	2	—	24
102–103°	16	3	—	—	19
104°— or higher	—	3	—	—	3
Total cases with fever	33	11	2	0	46
Total cases observed	61	13	8	0	82
Fifth to tenth days					
100–101°	15	1	2	—	18
102–103°	11	4	—	—	15
104° or higher	—	3	—	—	3
Total cases with fever	26	8	2	0	36
Total cases observed	61	8	7	0	76

*100°F. or higher.

and this cleared within a few hours following intravenous fluid administration.

Severe nausea was attributed to sulfadiazine in one case and vomiting was attributed to sulfathiazole in another. These symptoms began early and cleared rapidly when the drug was stopped. Leucopenia was encountered in 2 cases. In Case 47, the white blood cell count was 4,000 on the thirteenth day which was 1 day after the drug had been stopped. In Case 54 the total white count was 2,000 on the twelfth day, 2 days before the drug was stopped. The count in this case rose to 16,000 on the fifteenth day without any special treatment directed at the leucopenia. The total dose used was 54 grams in 12 days in the former and 79 grams in 14 days in the latter. In neither of these cases was the percentage of granulocytes depressed.

On the whole, therefore, it may be said that the incidence of untoward effects of chemotherapy was very low. Excluding the cases of hematuria and the 1 case of colic these toxic effects were not serious. It is possible of course, that other minor toxic effects were overlooked or that some of the symptoms ascribed to other factors may have been due to the drug. It is fair to say, however, that more serious complications and larger numbers of them were probably avoided by careful vigilance.

RESULTS

Any attempt to evaluate the effects of chemotherapy in the prevention or control of infection in the present group of cases must, of necessity, be little more than an expression of opinion or of impressions. Even the estimation of the presence, extent and severity of infection was beset with considerable difficulties. As to the burned surfaces, their appearance, odor, and the presence of purulent exudate containing bacteria, or the development of lymphangitis or cellulitis in the vicinity of the burns were relied upon to give evidence of infection. The significance of that infection, however, could not readily be determined in each instance. Healing apparently proceeded rapidly in spite of such infection in many of the cases with superficial burns, while in others particularly in third degree burns the

infection undoubtedly contributed to the development of malnutrition and also considerably delayed the healing process. With regard to the pulmonary lesions also, it was not possible to determine in most instances, to what extent the physical signs and x-ray findings were the result either of the original injuries or of superimposed infections.

In order to obtain some idea as to the amount of infection present in these cases some of the objective findings will be summarized. The occurrence of fever and leucocytosis at various intervals after the injuries will be analyzed from that point of view. The available bacteriological findings will be presented and correlated with the other evidences of infection.

Fever. An analysis of the occurrence of fever in the patients who were in the hospital for 18 hours or longer is given in Table III. Of the 101 patients in whom data were available only 10 remained completely afebrile. One of these 10 patients died during the first day but the others had only minor surface burns or respiratory injuries. Only 1 of the latter cases received chemotherapy and this was given only during the first day.

Fever occurred very early in most of the cases with moderate or severe burns and in those with respiratory damage. In 85 of the 91 patients who had fever at some time during their course, an elevation of temperature to 100 degrees F or higher was recorded during the first or second day. In almost every instance the fever was associated with surface burns of varying extent. This early appearance of fever can hardly be attributed to infection. It did, however, contribute to the difficulties in recognizing the presence of infection which may have occurred during the first few days. The fever was usually of short duration. In about two-thirds of the cases it lasted for 4 days or less but the proportion of patients having such a short febrile course was smaller among the survivors and somewhat higher among the fatal cases, many of whom died during this period. In most of these cases infection probably played only a minor rôle. In the remaining cases the fever was probably due to infections which usually were limited to the burned surfaces.

The 8 patients who had fever for more than 2 weeks are of interest. In 6 of them the burns involved 20 per cent or more of the body surface. Of the 2 remaining patients one (Case 68) had burns involving only 5 per cent of the body but some of the areas were deep and badly infected. This patient had no respiratory tract involvement. In the other patient (Case 22), on the other hand, the surface burns were relatively clean but there was marked respiratory injury with massive atelectasis of the left lower lobe and probably pneumonia superimposed in that lobe, and these were very slow to clear. In very few other cases could persistence of fever be attributed solely to respiratory tract infections.

In all of the fatal cases there was fever throughout most of the first few days except in those patients who died very early. Among those who recovered and were treated with sulfonamides the proportion of patients having fever dropped progressively from 92 per cent in the first 2 days to 54 per cent during the third and fourth days and 43 per cent during the next 6 days. Among the 13 patients who recovered but did not receive sulfonamides only 5 had any fever. These patients, however, had only minor surface burns and no respiratory tract involvement, and in no instance did their temperature rise above 101 degrees F.

The maximum temperatures observed were usually not very high. In more than half of the cases it was less than 102 degrees F. and in all but 12 of the remaining cases it was below 104 degrees. Those in whom the temperature rose to 104 degrees or higher are of special interest. Of the 8 who had such high fever during the first 48 hours, only 1 survived. This was a patient (Case 24) with a burn of 14 per cent of the body and a moderately severe (Grade 3) respiratory tract involvement. There was infection of the burned area later in this case but probably little if any infection of the respiratory tract, and the temperature levels were lower after the second day. The remaining 7 patients all died before the end of the second day. The temperature before death reached 106 degrees in 2 of them; 107.5 degrees in the third, and 109 degrees in a fourth.

TABLE IV.—MAXIMUM LEUCOCYTE COUNTS OBSERVED AT INTERVALS DURING THE FIRST 3 WEEKS IN VICTIMS OF THE COCOANUT GROVE FIRE

Maximum leucocyte count	Days after admission				
	1–3	4–7	8–14	15–21	1–21
Less than 7500	2	3	10	5	3
7500–9900	14	5	13	7^{1}	9^{1}
10,000–12,400	14	11^{1}	9	6^{1}	20
12,500–14,900	13^{1}	5^{1}	3	7	13^{1}
15,000–19,900	16^{3}	9^{2}	6^{1}	1	21^{4}
20,000–24,900	6^{2}	2^{1}	1^{1}	3^{1}	6^{2}
25,000–29,900	3^{2}	—	3^{1}	—	4^{2}
30,000 or higher	1^{1}	—	2^{2}	1	3^{2}
Total (cases)	69^{11}	35^{3}	47^{5}	30^{5}	79^{12}

Superscripts denote numbers of fatal cases included.

Of the 3 patients whose temperature reached 104 degrees or higher during the third and fourth day, one died on the fifth day with a terminal rise to 106 degrees; a second patient died on the sixth day, his temperature having remained at 104.5 degrees until his death, and the third died after 3 weeks. Only 1 patient had a rise in temperature to 104 degrees for the first time after the fourth day and this patient died on the thirteenth day.

In this series of cases, therefore, all but 1 of the 12 patients whose temperature at any time reached 104 degrees or higher, died and most of these deaths occurred in the first 2 days in patients with severe, extensive burns.

Leucocytosis. A total of 350 white blood cell counts were recorded during the first 3 weeks in 79 of the patients. Only an occasional count was taken in some while frequent counts were done in others. In most of the cases in which infection was suspected and in those in which there was persistent fever, counts were done at frequent though irregular intervals. An analysis of the occurrence of leucocytosis during the first 3 weeks in these 79 cases is shown in Table IV.

There was a definite leucocytosis in the majority of cases studied at each of the intervals listed. All but 1 of the 12 fatal cases in whom white blood counts were done had a leucocytosis, and in half of them the total count was over 20,000 at one time or another.

TABLE V.—EXTENT OF THE BURNS IN 28 PATIENTS IN WHOM INFECTION OF THE BURNED AREAS WAS NOTED

Per cent of body surface	Total area of burn	Deep (third degree) burn
Less than 5	2	11
5–9	10	4
10–19	5	3
20 or more	11*	7*
Total	28	25†

*Includes 5 fatal cases in which infection was noted.
†In 3 cases there were no third degree burns.
The figures in the last 2 columns indicate number of cases.

Such high counts were observed in only 7 of the 67 recovered cases included in this group.

The interpretation of these findings is not entirely clear. The frequency with which leucocytosis occurred early and the high counts that were found in some of the patients who died during the first 4 days without showing any definite evidence of infection, suggests that the early leucocytosis was primarily a reaction to the thermal injuries. On the other hand, infection was probably the main factor responsible for the elevated leucocyte counts that were noted during the latter half of the first week and thereafter.

Wound infections. There were only 2 cases in which the presence of infection in the burned surfaces was recognized and recorded on the third day. In most instances such infection was first recognized between the fifth and eighth days and in many cases it was not noted until several days later. A total of 28 patients were noted as having infections of their wounds. These infections were recognized by the appearance of the burned areas, the presence of purulent exudate and in some instances by the foul odor of the dressing. It may be presumed that minor infections occurred in other cases and were not recognized or recorded. In many of the cases infection appeared to be quite superficial. In a few instances the removal of foul-smelling dressings was followed by a sharp drop in temperature and improvement in the general condition of the patient. The total extent of burns in the cases which were infected is shown in Table V and the number of patients having third degree burns of various extent are also indicated. From this table it is seen that while some of the patients with infected

burns had relatively small areas involved, half of them had severe and deep burns involving 5 per cent or more of the body surface, and in 7 patients there were third degree burns of more than 20 per cent of the surface area.

Deep cellulitis and lymphangitis was recognized in only 1 case (Case 69) in which there was a relatively small and what seemed to be a superficial area involved. There may have been others in which it was not possible to differentiate underlying cellulitis from the inflammatory reaction to the burn. There were no other instances, however, in which lymphangitis or regional adenitis was observed.

In view of the difficulties in evaluating the factor of infection in the respiratory tract in the present cases, it is of interest to note the severity of the respiratory injuries in the 28 cases with infection in the burned areas. Only 3 of these 28 cases, including 1 fatal case, had no respiratory tract involvement. Clinically, 15 patients were considered as having mild to moderate damage in the respiratory tract and these included 2 fatal cases in which moderately severe involvement of the lungs and respiratory passages was found at autopsy. The remaining 10 patients, 1 of whom died, had severe symptoms of respiratory tract involvement. It is such cases that offered the greatest difficulty in determining whether the fever, leucocytosis, anorexia, and other symptoms of infection were due to the condition of the wound or whether additional infection of the injured respiratory tract also contributed to these manifestations.

Bacteriology of the infected surface burns. Bacteriological studies did not form a part of the "Burn Project" as set up at the Boston City Hospital and such studies were not made routinely in the Cocoanut Grove cases. Cultures of the infected surface burns were made in only 15 of the cases and unfortunately none of these was done in the early stages. In most instances the first culture was taken during the end of the second week or later, at a time when the local infection was well established. In some of these patients chemotherapy was still being administered at the time, while in others the sulfonamides had been discontinued either completely or temporarily. Since the infection was first noted in almost every instance while sulfonamide treatment was still being given and since the flora of the infected wounds was essentially the same irrespective of whether the chemotherapy was being continued, it is fair to assume that most of the surface infections developed under the sulfonamide treatment and were not affected by it.

The results of the cultures of the infected burns together with some of the relevant findings concerning the chemotherapy in the cases from which these cultures were obtained are shown in Table VI. The blood sulfadiazine levels obtained on the same day as the cultures were all comparatively low. This may have been a contributing factor in the establishment of infection in some instances. Higher levels, however, had been obtained in most of the same patients during the earlier stages of treatment at a time when these infections presumably were becoming established.

The organisms which were identified from the growth of these cultures are of some interest. Foremost among them was Staphylococcus aureus. This organism was obtained in abundant growth from almost every one of the cultures, and in most instances it was the predominant organism. Beta hemolytic streptococci were grown on one or more occasions in 9 of the cases. Pyocyaneus bacillus was obtained in 10 of the cases and proteus bacillus and diphtheroids were also obtained in some of the cases. Many of the wounds from which the gram negative bacilli were grown had a foul odor. Those from which pyocyaneus bacilli were obtained had the characteristic green color in the purulent exudate. Of some interest also was the isolation and identification of Friedlaender's bacillus on 1 or 2 occasions from each of 3 cases. Bacillus welchii was obtained from the surface cultures in 2 cases but there was no gas gangrene recognized clinically in these or in any other cases.

Complete biological and serological identification was not carried out on all of the strains obtained. The strains of Staphylococcus aureus which are listed in the table were all hemolytic and coagulase positive. The streptococci were identified only with respect to their hemolytic characteristics. In a few cases alpha hemolytic streptococci were obtained along with strains which showed beta

TABLE VI.—BACTERIOLOGICAL FINDINGS IN THE INFECTED SURFACE BURNS IN RELATION TO SULFONAMIDE THERAPY

Case No.	Per cent of surface burned		Chemotherapy			Day of culture	Blood S.D. level	Location of infected burn	Organisms found
	Total	Third degree	Day begun	Day ended	Total, grams				
9	5	1	2	16	83	12	7.0	Back of hand	S.au.; B.pyoc.; Str.α; Diphtheroids
11	16	2	2	28	155	13	2.4	Hand	S.au.; Str.β; B. coli
						16	—	Hand	S.au.; Str.β; B.coli; B. morgani
15	20	7	2	8	38	12	0	Hand	S.au.; Str.β; Str.α; B.proteus; B.coli; Diphtheroids
			12	16	25	24	—	Hand	B.coli; S.au.; B.pyoc.; B.morgani; B.fecalis alkaligenes
						38	—	Hand	Str.β; B.coli; S.au.; B. proteus
						53	—	Leg	Str.β; B.proteus; Diptheroids
17	30	15	2	15	86	50	—	Scalp	S.au.; Str.β; S.albus; B.proteus; Diphtheroids
			48	54	24	53	—	Scalp	B.M.C., Type B; S.au.; Str.β
			73	76	17	93	—	Graft-secretion	S.au.; B.proteus; B.pyoc.
						96	—	Graft-secretion	S.au.; Str.β; B.proteus; B.pyoc.; S.albus
28	25	5	3	13	55	17	—	Back	B.pyoc.; S.au.; Diphtheroids
						21	—	Back	S.au.; Str.β; Str.α; B.welchii; Diphtheroids
35	5	1	3	9	27	24	—	Hand	B.pyoc.; S.au.
38	55	45	3	22	108	36	—	Trunk	B.pyoc.
			32	44	48	49	—	Trunk	B.proteus; B.pyoc.; S.au.; Str.β
51	28	16	1	18	85	12	1.9	Hand	S.au.; B.proteus; Str.β; Diphtheroids
59	8	3	3	14	58	35	—	Right hand	B.proteus; S.au.; S.albus; Str.α; Diphtheroids
						35	—	Left hand	B.proteus; S.au.; S.albus; str.α B.coli
						45	—	Hand	S.au.
65	6	1	1	13	74	38	—	Grafted area	S.au.; Str.β; B.M.C., Type B
						45	—	Leg	S.au.; Str.β
						45	—	Hand	S.au.
68	5	1	1	13	67	17	0	Right hand	Str.β; S.au.; B.coli; Diphtheroids
			41	67	120	17	—	Left hand	S.au.; B.pyoc.; Diphtheroids
69	0	0	2	19	102	14	—	Hand	B.pyoc.; Str.α; S.au.
109	30	20	2	20	105	13	5.9	Back	B.pyoc.; S.au.; Str.β
						51	—	Back	S.au.; Str.β; Diphtheroids
						59	—	Grafted area	S.au.;B.M.C.; Type B; B.pyoc.; Str.α
						63	—	Grafted area	S.au.; Str.α; Enterococci; B.M.C., Type B
110*	30	30?	1	10	49	19	2.8	Ear	B.pyoc.; B.proteus; S.au.
			13	21	33	19		Right shoulder	B.pyoc.; B.proteus; S.au.; Str.α; B.welchii
						19		Right flank	B.pyoc.; B.proteus; S.au.; Str.α; B.welchii
						19		Left shoulder	B.pyoc.; B.proteus; S.au.; Str.α
128	30	20	2	29	160	20	5.1	Back	S.au.; B.pyoc.; B.proteus; B.coli; Diphtheroids
			39	48	54	40	—	(Blood culture)	B.morgani
			76	80	24				

*This patient died on the 28th day. Many blood cultures taken during life were negative. S.au. was cultured from the lungs at autopsy.

Explanations and abbreviations:

For definition of grades of respiratory involvement see Table I.

Days=days after admission (Nov. 20=day 1, etc.)

Blood S.D.=blood concentration of free sulfadiazine in mg./100 ml. on day culture was made (or within 1 day); —=not done.

Sputum: muc.=mucoid; pur.=purulent; epith.=epithelium; squam.=squamous; col.=columnar; B.S.=blood streaked; phag.=cells showing phagocytosis of bacteria.

Bacteriology: Str.=non hemolytic streptococci; Str.α=α hemolytic streptococci; Str.β=β hemolytic streptococci;
Pn.=pneumococcus (type given in Roman numerals); No./H.P.F.=number of encapsulated pneumococci per high power field as seen in Neufeld preparation;
S.au.=coagulase positive, hemolytic, staphylococcus aureus;
H.inf.=Haemophilus influenzae;
B.pyoc.=Bacillus pyocyaneus; G—=gram negative;
M.cat.=Micrococcus catarrhalis;
Percentages shown represent an estimate of the relative numbers on surface cultures (and smears); when not mentioned, the organisms are listed in the order of their relative frequency.
B.coli all were classified as B.coli communior.
B.M.C.=Bacillus mucosus capsulatus (Friedlaender's bacillus).

hemolysis while in others the alpha hemolytic streptococci occurred independently. The Friedlaender's bacilli were all identified as Group B.

Blood cultures were taken during the febrile course in many of the cases and most of them were sterile. Staphylococcus albus was recovered from blood cultures in 2 cases, diphtheroids in 1 case, and gram negative bacilli in 3 others. The significance of these findings is not certain but the organisms were considered at the time to be contaminants since other blood cultures in the same cases were negative. In Case 131, cultures of the infected wounds were not made but pyocyaneus bacillus was obtained from a culture of the blood on the eighth day. Earlier and later blood cultures in this case were negative.

Bacteriology of the sputum. Bacteriological studies of sputum were made on 1 or more occasions in 13 cases, including 3 in which cultures were also made of the wounds. In 10 of the cases there were severe grades of respiratory involvement. The sputum specimens were obtained from the patients after the mouth and pharynx were cleared by rinsing and gargling with tap water. They were taken directly to the laboratory where they were streaked on the surface of blood agar plates, grown in blood broth and injected into mice. Gram and Wright stained smears were made directly from the sputum, and Neufeld typing was carried out when organisms resembling pneumococci were seen. In contrast to the wound cultures those of the sputum were made during the first 2 weeks and while the patients were still receiving sulfonamides. The character of the sputums and the results of the bacteriological studies are listed in Table VII together with a summary of the significant features concerning the chemotherapy employed in the cases.

Most of the sputum specimens obtained early were quite scant, mucoid, and slightly purulent, and smears showed numerous squamous and sometimes ciliated epithial cells. Some of the later ones were frankly purulent and had either a yellowish, greenish, or chalky appearance. In 4 cases, some of the specimens were either rusty, blood-streaked, or pink in color due to admixture of blood.

As was the case in the wound cultures, the organism found with the greatest regularity and in the greatest numbers in the sputum was Staphylococcus aureus. This organism was cultured from almost every specimen obtained from 12 of the cases and it was the predominant organism found in many of these cultures. All of the strains were hemolytic and produced coagulase.

The streptococci obtained from the sputum were predominantly alpha hemolytic, and some nonhemolytic strains were also found. These were considered to be part of the normal mouth flora although in some instances they constituted one-half or more of the colonies that grew in the direct cultures on blood agar plates. Beta hemolytic streptococci were obtained only in Case 36, but although they appeared in considerable numbers, there was no clinical evidence of anything which could be interpreted as a hemolytic streptococcal infection in this case.

Pneumococci were obtained in significant numbers in 5 cases. In 3 of them types III, VIII, and XXIV pneumococci were obtained only in the first specimen and in 1 case type IV pneumococci were obtained in the first 2 specimens of sputum and no pneumococci could be found in any subsequent specimens. In the fifth case type XXII pneumococci were identified in large numbers in 4 of the 5 specimens studied. In some instances the pneumococci showed evidence of drug action in the stained smears made directly from the sputum. From each of the specimens containing pneumococci other organisms, particularly staphylococci, were also obtained in large numbers.

Influenza bacilli were identified in one or more specimens from 4 cases, and miscellaneous other organisms were also encountered either in the smears or in the cultures.

The significance of any of these organisms and the part which they played in pulmonary pathology cannot be stated with any degree of certainty. The purulent character of the sputum in some of the cases strongly suggested that the Staphylococcus aureus which was so abundant was actually active and contributing to the necrotizing character of the lesions already present in the trachea and bronchi and possibly also in the lungs. Pre-

TABLE VII.—BACTERIOLOGICAL FINDINGS IN SPUTUM IN RELATION TO CHEMOTHERAPY

Case No.	Grade of respiratory involvement	Chemotherapy			Day of culture	Blood S.D. level	Description of sputum	Bacteriological findings
		Day begun	Day ended	Total, grams				
8	3	2	16	86	2	2.9	Muc.-pur.; B.S.; carbon; ciliated epith.	Str.α; Pn. III (10/H.P.F.); few S. au.
					9	7.2	Muc.-pur.; B.S.; carbon; squam. epith.	Str.(50%); Str.α(25%); S.au.(25%); no Pn.
					14	3.5	Frothy; muc.; rusty	Str.α(90%); S.au.(10%)
11	3	2	28	155	11	2.4	Muc.-pur.; rusty; phag. squam. epith.	S.au.(50%); Pn. IV (25/H.P.F.; 25%); H. inf. (25%)
					13	—	Muc.-pur.; rusty; epith. cells—phag.	H.inf.?(50%); Str.α(35%); S.au.(10%); Pn. IV (3/H.P.F.; 5%)
					19	—	Muc.-pur.	H.inf.(55%); S.au.(40%); Str.α(5%); no Pn.
17	1+	2	15	86	3	6.3	Frothy; muc.-pur.; phag. squam. epith.	Str.α(67%); H.inf.?(33%); Spirilla infusiform bacilli in smears
19	3	2	17	81	18	4.4	White; muc.-pur.	S.au.(50%); Str.α(50%)
		32	37	34	33	3.5	Chalky; pur.	S.au.; few Str.α
					38	—	Throat swab	Str.α(85%); S.au.(10%); B.pyoc.; G—diplo.
22	3	2	14	80	9	5.8	Yellow; muc.-pur.; squam. epith.	Pn. XXII(40/H.P.F.; 50%); S.au.(50%)
		26	31	25	12	5.0	Yellow; muc.-pur.	S.au.(75%); Pn. XXII(60/H.P.F.; 25%); rare Str.α
					13	5.0	Yellow; muc.-pur.	Pn. XXII(100/H.P.F.; clumped, "moth-eaten"); S.au.; G—rods
					17	0	Throat swab	S.au.; Str.α
					18	0	Muc.-pur.	S.au.(75%); Pn. XXII(many/H.P.F.; clumped; 25%)
29	2—	—	—	0	2	—	Black; muc.-pur;.; carbon; epith. cells	S.au.; few Str.α; Diphtheroids
37	3—	2	17	90	2	4.2	Muc.-pur.; B.S.; sheets of col. phag. squam. epith.	Str.α(50%); Str.β(20%); Str.(20%); Pn. XXXIV(20/H.P.F.; 10%)
					3	4.0	Muc.-pur.; sheets of phag. squam. epith. & polys.	Str.β(50%); Str.α(45%); S.au.(5%)
63	1—	2	8	37	2	9.3	Scant; muc.-pur.	Str.αpredom.; H.inf.; few S.au.; few diphtheroids
64	3—	2	11	50	3	6.4	Scant; muc.-pur.	Str.α; M.cat.; S.au.; (rare fusiform bacilli & spirillae in smears)
					4	6.8	Scant; muc.-pur.	Str.α; M.cat.; H.inf.; diphtheroids; rare fusiform bacilli and spirilla
69	3	2	19	102	13	6.3	Muc.-pur.; phag. polys. & squam. epith.	Pn. VIII(75%); S.au.(25%)
					18	—	Frothy, muc.; loaded with organisms	S.au.; M.cat.; Str.α; Diphtheroids (25% each); no Pn.
91	4	1	18	93	18	—	Scant;, muc.; epith. cells & polys.	Few S.au. & Str.α
107	4	1	6	29	7	8.9	Muc.-pur. (bronchus at autopsy)	S.au.hem.; few diphtheroids
131*	4	2	11	36	11	2.1	Chalky, pink	Almost pure culture of S.au.; rare Str.α

For explanations and abbreviations see Table VI. *Blood culture on 8th day—B. pyoc.

sumably, the pneumococci also played a rôle in some of the cases.

As already indicated, it was difficult to determine the part played by infection in the abnormal physical and x-ray findings in the lungs. In many of the cases with extensive signs, fever and leucocytosis probably resulted from the skin lesions. This was particularly true in those cases in which infection of the burned areas was apparent. Most of the patients with extensive pulmonary lesions had fever and leucocytosis during part of their course and, with few exceptions, these evidences of infection improved with the healing of the surface burns. On the whole, considering the extensive amount of respiratory damage present at the time of admission in this group of cases, it may be stated categorically

that infections of the respiratory tract were relatively few and generally mild. Furthermore, it seems reasonable to ascribe this comparative mildness and infrequency of the respiratory tract infections to the chemotherapy which these patients obtained during the first week or two in the hospital.

There was also every reason to believe that none of the patients died primarily as a result of infection of the respiratory tract. There is one possible exception. This was a patient (Case 110) with severe and extensive burns who seemed much improved after 3 weeks of a rather stormy course. He was then transferred to another hospital for skin grafting and further care. He had no clinical evidence of pulmonary involvement when he left the hospital and x-rays at that time showed his lungs to be essentially clear. Soon after he arrived at the other hospital he developed high fever and respiratory distress and died 6 days later. Autopsy in this case showed an extensive necrotizing type of staphylococcal pneumonia and evidence of the underlying tracheobronchial damage which was similar to that found in other cases. Definite evidence of early confluent staphylococcal pneumonia was also present in Case 107. In this case a tracheotomy was performed early and death occurred on the seventh day and resulted from respiratory obstruction. In the other fatal cases infection played only a minor rôle in the pathology of the respiratory tract as found at autopsy.

CASES ILLUSTRATING THE USE OF CHEMOTHERAPY

It has already been indicated that the urgent needs of patients made it difficult and at times impossible to make and record a considerable number of observations which would have been useful for the purpose of evaluating many important features of the various types of cases encountered. This is particularly true with respect to the evaluation of the results of the various therapeutic agents and procedures used. After the initial phases, however, a number of studies were made and some of them are of interest in spite of the paucity of earlier data. Because of the peculiar problems presented in the administration of sulfonamides in many of the cases from the Cocoanut Grove fire, studies of this aspect were undertaken in representative cases as soon as it became feasible. The results of the studies will be presented by summarizing the findings in characteristic cases in which there were various combinations of surface burns and respiratory injuries of different degrees of severity. The data in these cases will be shown in the accompanying figures.

Cases of hemoglobinuria and impaired renal function. Among the first problems encountered during the initial survey of the cases for the purpose of outlining a program of chemotherapy were the scant urinary outputs and their association with hemoglobinuria in a few of those who were most severly burned. As already stated, this finding prompted the use of alkalis which were given at the time with the view of preventing or minimizing renal complications from that source. This procedure seemed justified because of the high acidity of the urine in these cases, but the possibility of water retention was borne in mind. Attempts were, therefore, made to keep track of the fluid balance as far as possible. It was the finding of hemoglobinuria and oliguria which prompted the excessive caution and delay in initiating sulfonamide treatment in some of the cases, at least until alkalis had been given and a reasonable output of urine assured.

Details concerning the hematologic and other interesting findings in these cases as well as studies dealing with the mechanism of hemoglobinuria are given in the paper by Shen, Ham, and Fleming. Most of the Cocoanut Grove cases in which this complication was recognized died early. The observations relevant to the chemotherapy in 4 of the fatal cases with hemoglobinuria in which death occurred on or after the fourth day, are shown in Figure 2 and the findings in the only patient admitted from this fire who survived this complication are shown in Figure 3. Each of these 5 patients had burns which involved 45 per cent or more of their body surface and were mostly third degree. Shock was present on admission in Cases 119, 125, and 131 while in others it was averted in the early phases by vigorous treatment with plasma and fluids.

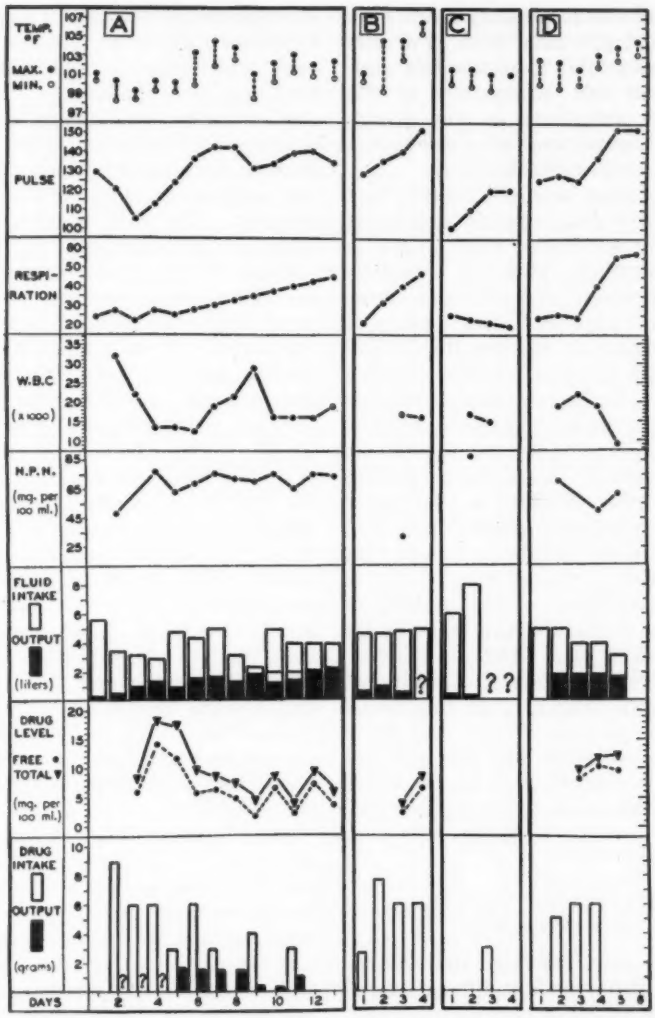


Fig. 2. Findings in 4 fatal cases with hemoglobinuria. A, Case 131; B, Case 119; C, Case 120; D, Case 125.

During the first 24 hours each patient received between 3 and 5 liters of fluid mostly by the intravenous route, in addition to the large amounts of plasma. Large amounts of fluid and varying amounts of plasma were also given during the succeeding days. Only 1 of these patients, however, excreted a significant quantity of urine during the first day (Case 38, Fig. 3) and he continued to maintain a fairly good output. In Case 125 (Fig. 2D), there was a good output of urine on the second day and thereafter; in Case 119 and Case 120 (Figs. 2B and 2C respectively) the output continued to be small while in Case 131 (Fig. 2A) it improved steadily over a period of 4 days.

Sulfadiazine was started at the end of the first day in Case 119, during the second day in Cases 125 and 131 and early in the third day

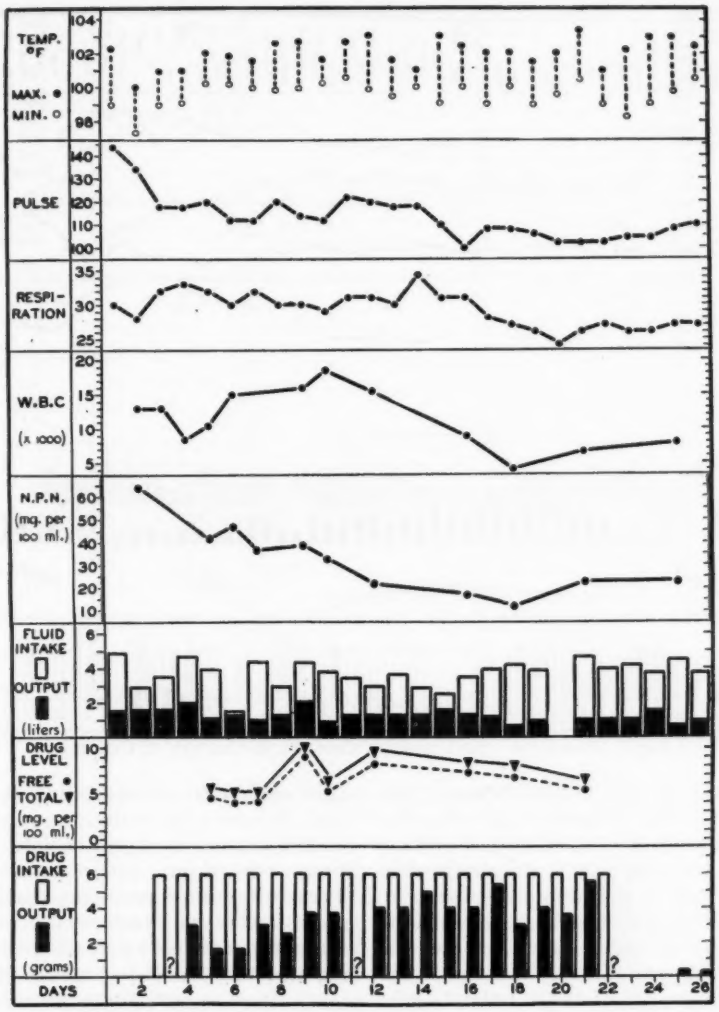


Fig. 3. Findings in Case 38 in which there were extensive burns, hemoglobinuria, and recovery.

in Cases 38 and 120. The initial dose was given intravenously except in Case 38. Treatment was not continued in Case 120 because of the poor condition of the patient and the failure to establish a good urine flow. The rest of the treatment varied in different cases as shown in the charts.

There was an elevation of the blood nonprotein nitrogen in all but 1 of these cases and this finding contributed to the caution observed in the administration of the drug. It is interesting to note, however, that this abnormality was not associated with excessive drug retention or with a high degree of acetylation of the drug in the blood, except temporarily in Case 131. In that case and also in Case 125 the blood nonprotein nitrogen remained elevated at a fairly constant level over several

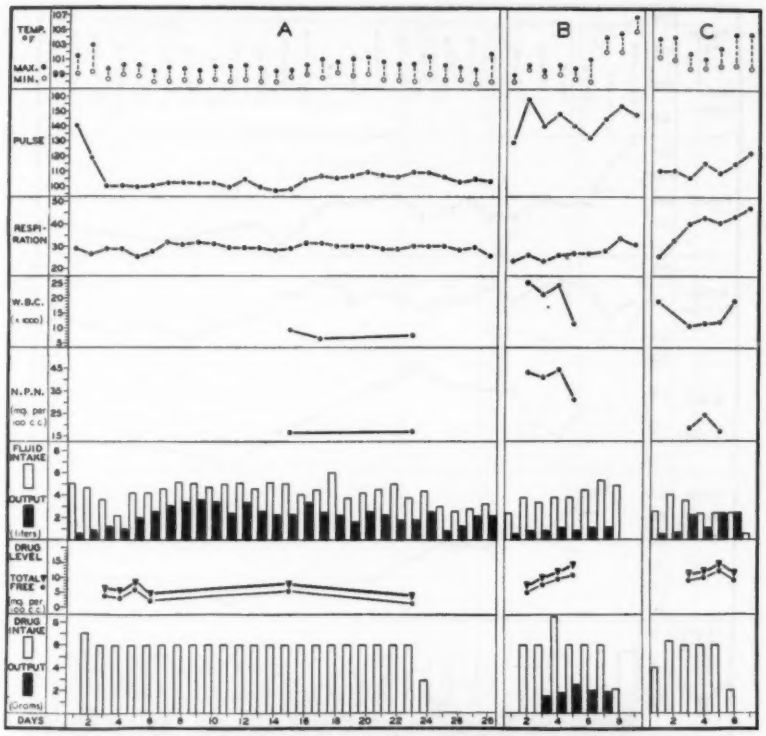


Fig. 4. Findings in 3 fatal cases. A, Case 128; B, Case 113; C, Case 107

days, while in Case 38 the level dropped progressively to normal. Moderate blood sulfadiazine levels were maintained in each of these cases, but it was necessary to reduce the dose to avoid excessive drug retention in Case 131.

Fever, tachycardia, and leucocytosis were present in each of these cases. In 3 of the fatal cases there was a steady increase in the respiratory rate. All of those patients who died had extensive tracheobronchial and pulmonary lesions but evidence of some bronchopulmonary infection was found at autopsy only in Case 131. There was definite infection of the wound in Case 131 and in Case 38.

Other fatal cases. The findings in 3 other fatal cases of different types are shown in Figure 4. All of these patients were in shock during the first few hours in the hospital. In Case 107 (Fig. 4C) there was a burn of moderate severity involving 12 per cent of the body surface but there was marked tracheobronchial obstruction necessitating early tracheotomy, frequent aspirations and the continuous administration of oxygen which, from time to time, was given under positive pressure. These procedures gave only partial and temporary relief. In each of the other 2 cases there were extensive and severe burns involving an estimated 30 per cent of the body surface. In Case 128 there were no abnormal physical signs or symptoms referable to the respiratory tract, while in Case 113 there was considerable respiratory distress without any definite symptoms of obstruction.

In each of these cases there was only a small urine output during the first 24 hours in spite of the administration of moderate amounts of fluid. Sulfadiazine was begun at the end of the first day in Case 107 and early in the second day in Cases 113 and 120. The intravenous route was used for the initial dose and for an occasional follow-up dose in the latter 2

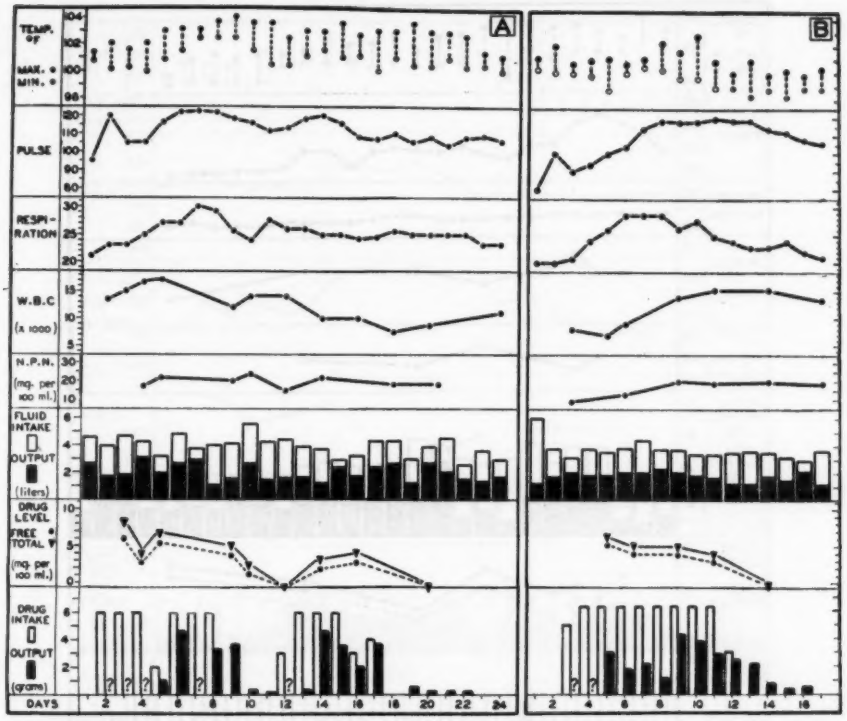


Fig. 5. Findings in 2 cases with fairly extensive burns and recovery. A, Case 15; B, Case 28.

cases whereas oral doses were used throughout in Case 120.

Slightly elevated nonprotein nitrogen levels were found only in Case 113. Drug concentrations were maintained at a low level in Case 128 and at moderate levels in Case 107 while the initial levels were low and increased gradually in Case 113. There was some difficulty in maintaining good urine output during the first days in each case. There was probably some water retention in Cases 107 and 113 during the last 2 or 3 days. This was evidenced by the finding of dependent edema.

There was only minor infection found in the lungs at autopsy in Case 113 and some confluent bronchopneumonia in Case 107 but both had rather extensive tracheobronchial and pulmonary pathology. In Case 128 death occurred on the eightieth day and was attributable to malnutrition. The lungs in that case remained clear throughout but there was considerable infection of the wound off and on after the first 2 weeks.

Cases of fairly extensive burns and recovery. The findings in Cases 15 and 28 are shown in Figure 5. In the former, the burn involved 20 per cent of the body surface and in the latter it involved 28 per cent and the patient was in shock at the time of admission. A good fluid balance was readily established in both of these cases. They both had only minor respiratory involvement and this was limited mostly to the upper respiratory tract.

Sulfadiazine treatment was started early in the second day in Case 15 and during the third day in Case 28 and all the therapy was given orally. In the latter patient the therapy was maintained for about a week while in the former it was given with interruptions over a 2 week period. Low grade infection developed in the wounds during the latter part of the treatment and persisted for several weeks in

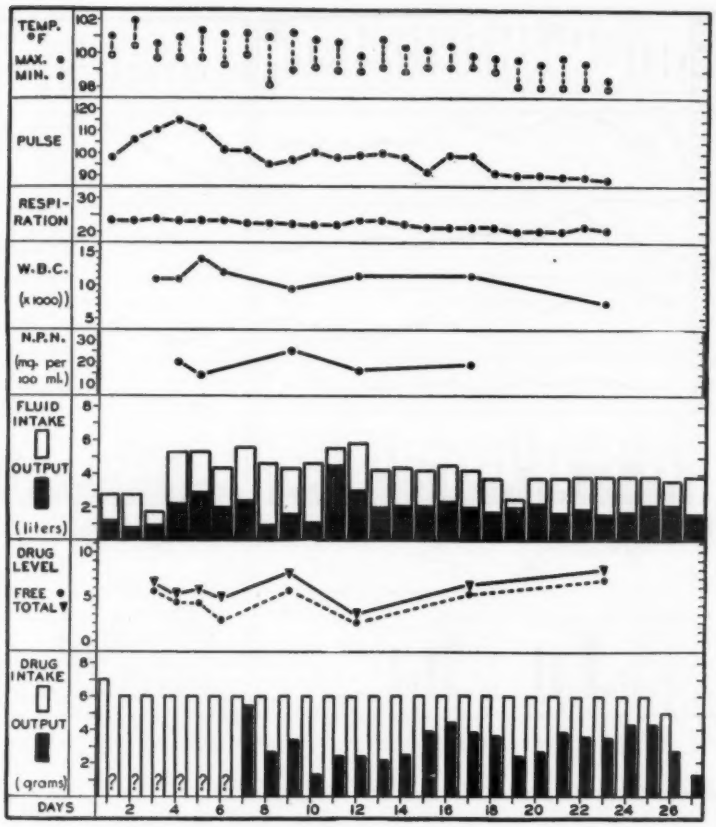


Fig. 6. Case 11.

both of these cases. The respiratory tract, however, remained free of infection as far as could be determined.

Cases of severe respiratory tract damage and surface burns of moderate extent. The data in 3 such cases, Cases 11, 22, 24, are shown in Figures 6, 7, and 8, respectively. The burns involved 16 per cent of the body surface in Case 11; 6 per cent in Case 22 and 14 per cent in Case 24. While a small part of the burns were deep in the first 2 cases, most of the involved areas in Case 24 proved to be third degree burns. None of these patients were in shock. Each of them received 2.5 to 3 liters of fluid in addition to plasma during the first 24 hours. There was a small output of urine during that period in Case 24 but each of the others excreted more than a liter during that time.

Full oral doses of sulfadiazine were started shortly after admission in Case 11 and on the second day in the other 2 cases. This treatment was maintained for more than 3 weeks in 2 of the cases while in Case 22 it was interrupted after 2 weeks and then given again for a few days after an interval of a week. The blood levels in these cases remained fairly low most of the time. This may have been due, in part, to the fairly large amounts of fluid taken by these patients throughout most of this period. There was no significant increase in the blood nonprotein nitrogen in any of these cases.

Each of these 3 patients had some fever and elevated pulse rate. The fever was low grade

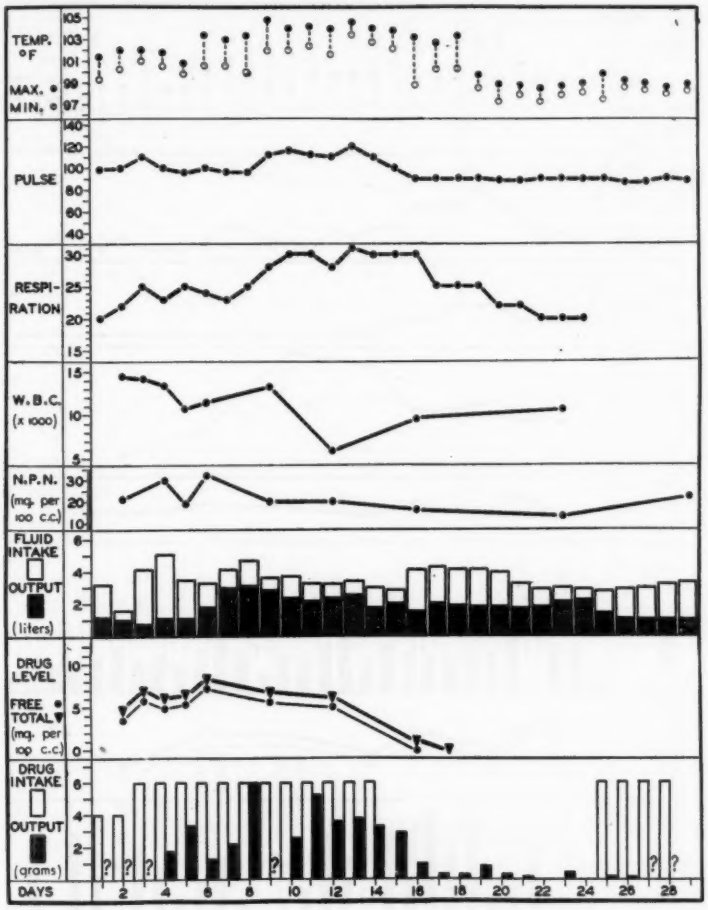


Fig. 7. Case 22.

and declined steadily during treatment in Case 11 and the patient raised some purulent and rusty sputum containing staphylococci, pneumococci, and influenza bacilli (Table VII). During this time there were diffuse musical and crepitant râles limited mostly to the lung bases but there were no extensive areas of consolidation. There was also slight infection of the wound which was first noted during the latter part of the second week. In Case 22 the temperature and pulse rose during the latter half of the first week and remained elevated for 2 weeks. During this period there were definite signs of consolidation and massive atelectasis of the left lower lobe and the patient raised moderate amounts of mucopurulent sputum containing many pneumococci and staphylococci (Table VII). The physical signs and abnormal x-ray findings persisted for more than 4 weeks and cleared only gradually thereafter. There was no definite infection of the surface burns.

In Case 24, on the other hand, there was moderate infection in the deeper burns. This was accompanied by fever and leucocytosis which began during the end of the first week

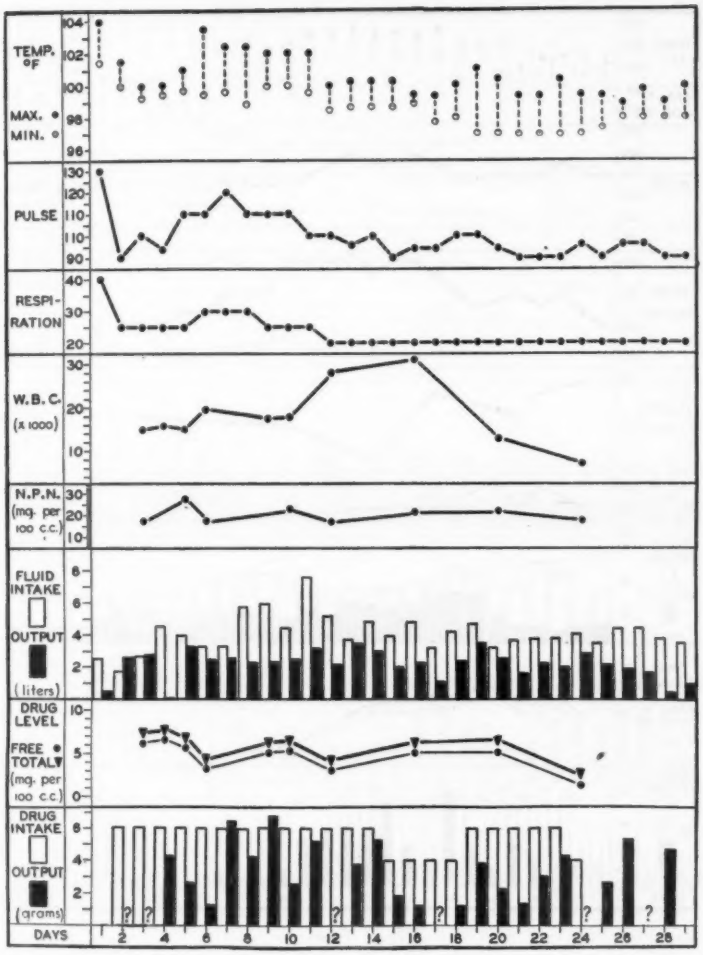


Fig. 8. Case 24.

and persisted at lower levels for several weeks. There were extensive signs in the lungs in this case at the time of admission and these cleared gradually, but there was no definite evidence of pulmonary infection.

Cases of severe respiratory tract involvement and minor surface burns. Data in 2 such cases are shown in Figure 9. One of these patients (Case 8) had a "chest cold" during the week before the fire and had considerable respiratory distress associated with extensive musical and crepitant râles in the lungs during the first few days. The patient improved rapidly after chemotherapy was started although the signs in the lungs persisted for more than a week. In Case 53 the patient had a period of severe stridor during the first 2 days and this was accompanied by moderate fever, elevations of pulse rate, and signs of consolidation or atelectasis of the lungs. All of these symptoms were completely relieved and the signs cleared rapidly after the second day following an episode of severe choking and coughing during which the patient raised a large fibrin cast of

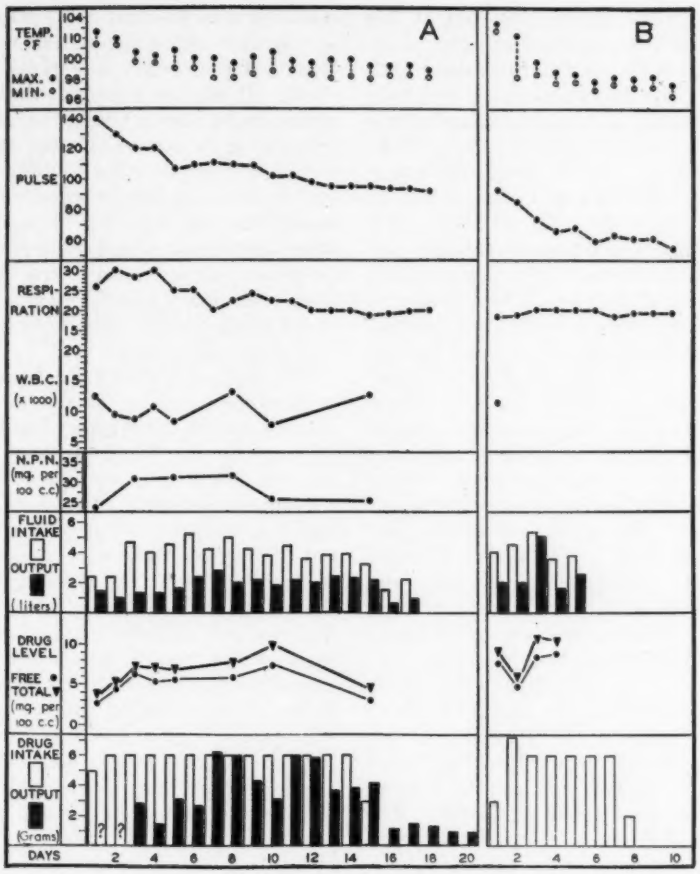


Fig. 9. A, Case 8; B, Case 53.

the trachea. The patient continued to improve steadily after this episode. His lungs cleared rapidly and there was no further evidence of respiratory tract infection.

EVALUATION

The chief purpose of this presentation was to summarize the objective findings which are available concerning the chemotherapy used and the evidence of infection found in the patients admitted to the Boston City Hospital from the Cocoanut Grove fire. The experiences in the present cases has brought out a number of points which are worth considering briefly.

The difficulties encountered in administering chemotherapy in many of the present cases have been brought out and perhaps overemphasized, but advisedly so. The problem of shock and the possible damage to the kidneys in cases of severe burns contribute major problems to the maintenance of adequate renal function. These factors constitute an essential part of sulfonamide chemotherapy particularly since it seems desirable to maintain fairly high blood levels of the more potent drugs, such as sulfathiazole or sulfadiazine, which also happen to be only slightly soluble. This aspect of the chemotherapy of burns and wounds has received some consideration in

connection with its topical use, but it has either been taken for granted or ignored by most observers with respect to systemic administration of the sulfonamides. The latter, too, requires careful and individualized attention to details if one is to use these drugs intelligently and be able to assess their true value. These difficulties and the failures of chemotherapy with the sulfonamides which are now available justify a continuation of the efforts to obtain less toxic and more readily controllable as well as more effective agents.

In the present cases it is not possible to give any true evaluation of the effect which chemotherapy had in preventing or limiting infection. There are, of course, no controls for comparison. Indeed, there are few similar groups of cases with which such comparisons can be made. At the Massachusetts General Hospital emphasis was placed on strict aseptic technique, and eschar producing agents were scrupulously avoided. In this hospital, on the other hand, aseptic precautions were not rigidly enforced, and tanning agents and dyes were applied to the burned surfaces in many of them. Nevertheless, the frequency and severity of the wound infections were apparently quite similar in the Cocoanut Grove cases at both institutions. Whether or not infection of the wounds would have been more severe had sulfonamides not been used at all can only remain a matter of conjecture. The almost complete absence of septicemia, lymphangitis and extensive cellulitis beyond the confines of the burned areas in spite of the extensive and severe lesions may probably be attributed, in part at least, to the systemic use of these drugs. Local infections limited to the burned surfaces, on the other hand, were certainly not prevented. In this respect the results are similar to those obtained under the more carefully controlled condition in the study summarized in Meleney's report (5).

With respect to the respiratory injuries, on the other hand, the comparatively small number of severe pulmonary infections can probably be attributed directly to the use of the sulfonamides. The fact that so few of the patients with severe respiratory damage died after the first few days, coupled with the additional fact that those in whom death occurred after the first 2 or 3 days, had extensive surface burns, can be taken as an indication that pulmonary infections were kept in check. It may be expected that the sulfonamides might have a similar beneficial effect in preventing or controlling the late infectious complications of other pulmonary irritants such as those used in chemical warfare or those sometimes encountered in industry. In 2 other disasters in which respiratory tract complications occurred from fire or irritants or both, pulmonary infection was a major factor in all of the deaths which occurred after the first 2 to 3 days (2, 7).

The organism which was most frequently encountered in the infections of both the wounds and the respiratory tract was Staphylococcus aureus. Most strains of this organism are only slightly susceptible to sulfonamides. Prolonged treatment with the maintenance of high blood levels are therefore probably essential if infection with these organisms are to be controlled. Once the necrotizing action of these organisms has occurred and purulent foci become established, such treatment, if successful, probably serves only to limit the spread of infection until the exudate is evacuated or local healing takes place. The low sulfonamide blood levels generally obtained both in the cases at this hospital and in those at the Massachusetts General Hospital, as well as the failure to pursue the treatment adequately may have been important factors in limiting or minimizing the effectiveness of the sulfonamide drugs. The reasons for the failure of sulfonamides to control the growth of bacteria in surface wounds have been adequately discussed by Lyons (3) and Meleney (5) among others.

It is possible that penicillin would have been more effective in many respects. Even with this agent, however, it is now recognized that small doses such as those used at the Massachusetts General Hospital are totally inadequate even for prophylaxis of infection when the Staphylococcus aureus or the other usual wound contaminants are concerned. Larger and more frequent doses may be more effective but this still remains controversial (1, 6). It is of interest that even hemolytic streptococci were grown from some of the

wounds in spite of the use of sulfadiazine at both institutions and the added use of penicillin at the Massachusetts General Hospital. Larger doses of penicillin might have been expected to prevent the growth of this organism in the wounds.

The chief advantage of penicillin which remains undisputed at this time is its almost complete freedom from toxic side effects when given systemically and probably also when it is used locally in moderate concentrations. This agent is also more effective against the staphylococcus and against many other gram positive organisms. These attributes are reflected in the improved general condition of the patients with severe and deep wounds after they are adequately treated with penicillin (4). The limitations of the value of penicillin lie in its failure to control the growth of many local wound contaminants and these contaminants may serve to reduce its effectiveness. It is to be hoped that other antibiotics will be found which are just as innocuous to the host but are more effective against a larger range of organisms.

One point of interest which was brought out in the analysis of the present cases may be mentioned briefly, namely, the prognostic significance of high fever and high leucocyte counts in patients with extensive burns. Almost all of the patients whose temperatures were over 104 degrees during the first few days died. Likewise, the mortality was high among those in whom leucocyte counts above 15,000 were obtained during the first week after the burns were sustained.

SUMMARY AND CONCLUSIONS

The available data concerning the use of sulfonamide drugs in the patients admitted to the Boston City Hospital from the Cocoanut Grove fire were presented. Chemotherapy, chiefly with sulfadiazine, was given only systemically for the purpose of preventing or controlling infection of the surface burns and of the respiratory tract. The management of the chemotherapy in many of the cases was complicated by the presence of shock and by the inadequate urinary output resulting from this or other causes. Treatment was continued in what are usually considered to be adequate doses for an average of 11 days. Blood levels were often irregular and were usually lower than those which might be considered desirable. Toxic effects were comparatively infrequent and mild.

It is not possible to evaluate properly the effects of the chemotherapy in the present cases. Infections of deeply burned areas occurred after the first week and were fairly frequent but not severe. Extension beyond the burned area was observed in only 1 case. Staphylococcus aureus was obtained quite regularly from the infected area and was usually the predominant organism. Hemolytic streptococci and various gram negative bacilli were also cultured from most of the wounds. The virulence of these organisms and their significance with respect to the wound healing varied considerably but was not possible to assess.

Pulmonary infections were few and usually mild. There was some evidence of infection in the lungs of the fatal cases, but extensive pneumonia was found in only 2 of them. Other patients had protracted respiratory symptoms and physical x-ray signs in the lungs, with fever and leucocytosis. It was difficult, however, to determine to what extent pulmonary infection was responsible for these manifestations, since similar signs and symptoms were noted early in most of the same patients and resulted from the injuries which were sustained. Furthermore, most of these patients also had extensive surface burns, and infections of these areas contributed to the fever and the leucocytosis. On the whole, it was considered that the chemotherapy was responsible, at least in part, for minimizing pulmonary infection and for preventing delayed deaths from pneumonia in many cases.

REFERENCES

1. CHURCHILL, E. D. Ann. Surg., 1944, 120: 268.
2. FISCHER, B., and GOLDSCHMID, E. Frankft. Zschr. Path., 1920, 23: 11.
3. LYONS, CHAMP. Surg. Gyn. Obst., 1942, 74: 571.
4. Idem. J. Am. M. Ass., 1943, 123: 1007.
5. MELENEY, F. L. Ann. Surg., 1943, 118: 171.
6. Idem. Bull. N. York Acad. M., 1944, 20: 517.
7. NICHOLS, B. H. Am. J. Roentg., 1930, 23: 516.
8. SHEN, S. C., HAM, T. H., and FLEMING, E. N. England J. M., 1943, 229: 701.

EXPERIENCE IN THE MANAGEMENT OF THE ABDOMINAL WOUNDS OF WARFARE

FRED J. JARVIS, M.D., F.A.C.S., Major, M.C., A.U.S., Seattle, Washington,
WALTER L. BYERS, M.D., Captain, M.C., A.U.S., Sheffield, Iowa, and
EDWARD V. PLATT, M.D., Captain, M.C., A.U.S., Haddon Heights, New Jersey

IN somewhat over a year since the Salerno landings, during the Italian and French campaigns, we have been privileged to operate upon 128 patients with abdominal wounds as a general surgical team of an auxiliary surgical group. During the early months of 1943 the senior author reviewed a series of 346 cases of the same type representing the early experience of the large group of surgeons of his organization. From these experiences, guided by the mature opinions of consultants in two theaters of war, and influenced constantly by close association with surgeons sharing the problems of forward surgery, we have evolved a plan of management which it would seem well to discuss at this time. Certain unsolved problems have also emerged, the presentation of which it is hoped may elicit aid in their solution by those working in experimental laboratories.

This work has been done entirely in field hospitals, representing the most forward echelon wherein definitive surgery may be performed; small hospitals in tents, geared exclusively to the care of "first priority" casualties: wounds of the abdomen, severe wounds of the chest, patients in shock from any cause including, therefore, many severe fractures, traumatic amputations, and major vascular injuries. Combined in these small, completely mobile hospitals of maximum bed capacity for 50 patients are all the real essentials for performing major surgery; a blood and plasma bank, a small laboratory, portable x-ray facilities, oxygen, experienced and thoroughly trained nursing and technical personnel, trained anesthetists equipped with portable apparatus for administering inhalation anesthesia, trained surgical assistants, and surgeons.

From the Second Auxiliary Surgical Group.

Thanks to the splendid co-operation of the medical staff of the division most patients have been received between 1 and 2 hours after being picked up on the battle field. The average time of admission following wounding has been 4.5 hours[1]. The major time loss has occurred on the battle field where it has frequently been impossible to reach the wounded soldier for some hours.

OPERATIVE POLICY

The evolution of the operative treatment of wounds of the abdomen by military surgeons has paralleled the development of abdominal surgery. It has been generally agreed by surgeons of this war that, with few rare exceptions, celiotomy and surgical repair are indicated in any wound involving the contents of the peritoneal cavity, and also in wounds of the extraperitoneal rectum in order to divert the fecal stream. With this in mind we have operated upon every patient regardless of risk, believing that even though there be but the slightest chance of survival, we have been unable to take the responsibility for decision not to operate. The occasional survival of a patient who has suffered what has appeared to be a "lethal wound" has strengthened us in this attitude. Fortunately, it has not been necessary long to delay operation or to deny operation entirely because of the press of casualties. Our records include 2 additional cases of patients treated conservatively, one with a tiny fragment entering the liver through the right chest, the second a prisoner patient admitted 3 days following the penetration of bladder and ileum through the buttocks with a small shell fragment, whose peritonitis seemed confined to the lower abdomen and pelvis and who died

[1] Excluding 1 patient admitted 3 days following wounding.

TABLE I.—TIME LAG IN RELATIONSHIP TO MORTALITY—110 CASES

Hours	No. patients	Lived	Died	Mortality per cent
0 to 6	40	28	12	30
6 to 12	54	38	16	31
12 to 18	10	7	3	30
18 to 24	5	4	1	20
Over 48	1	0	1	

3 days later of this peritonitis. Regardless of time lag it has proved profitable to operate upon all patients with intraperitoneal perforation of a hollow viscus (Table I). There have been a few patients admitted moribund who have expired within a few minutes of their admission. Of 547 abdominal and thoracoabdominal cases from the records of a field hospital over a 6 months period, 36 patients (6.5%) died prior to operation.

MORTALITY

Comparison of mortality rates with other reported series of abdominal wounds will not be made here because the source material for these figures is not available to us. Such comparison is likely to prove of little profit unless one takes into account several factors that may markedly influence such a statistical study. In the military situation wherein types of cases are selected for operation in the various echelons by process of triage the hospital in the first echelon to the rear of the most forward hospital finds that the majority of its peritoneal perforations are those that have been overlooked by triage officers further forward, or that the patient has been deliberately sent to the rear with relatively minor pathology, the patient in good condition. Death following operation on these patients is relatively infrequent. The inclusion of patients in whom no intraperitoneal perforation was found may likewise lower the mortality figure. Military policy and tactical exigency may not allow for holding the patient beyond the first 24 to 48 postoperative hours. Since over half the patients die subsequent to this time, mortality figures from the initial installation may give a very incomplete figure.

By the same token, comparison between military and civilian wounds of the abdomen must take into account their vastly different character. The complexity of the problems presented by the customarily multiple wounds produced by several high explosive missiles defies accurate description. Frequently concomitant head or thoracic wounds, transections of spinal cord, traumatic amputation of extremities, compound fractures of major long bones, injury to major vessels may place the patient's life in greater jeopardy than relatively minor intraperitoneal pathological conditions. It is impossible to correct mortality figures to take into account the contribution of concomitant wounds to death. Wounds caused by automatic small arms fire are likely also to be multiple. The large caliber and high velocity of the small arms weapons of warfare increases their lethal effect. Stab wounds of the abdomen, forming a high percentage of civilian experience, have not been encountered by us.

TABLE II.—TYPE OF MISSILE

	Number	Per cent Total	Died	Per cent mortality
High explosive fragment	97	74.6	29	29.7
Small arms	32	25.3	8	25.0
Undetermined	1		1	
Total	130	100	38	28.7

On the credit side of the ledger, in favor of the soldier casualty, are his relative youth, good health, and vigor prior to wounding. These are at least somewhat balanced by fatigue, poor nutrition in the combat situation, and exposure.

The mortality of 128 consecutive, unselected cases in which patients were operated upon was 23.4 per cent. Follow-up information now available on all but 8 of the patients who were evacuated has added 6 late deaths, making the corrected mortality figure 28.7 per cent (Table II).

DIAGNOSIS

The diagnostic problem is chiefly one of reconstructing the course of the missile. Michels has recently discussed this phase of the problem in detail. There are certain principles that should be reviewed.

1. Except in the occasional case in which resuscitative measures must be initiated immediately in order to save life, the patient should be thoroughly examined in a good light as soon as possible after admission in order to determine the course of treatment. Every first aid dressing is removed to expose the wounds. A rapid survey of the patient's shock situation, the condition of heart and lungs, and the sensorium is made. Urine and stomach contents are examined grossly for blood. The rectum is digitally examined in all wounds of the lower abdomen, pelvis, or buttocks, and the presence or absence of blood is noted. As soon as possible x-ray localization is made of the missiles. A tentative diagnosis is formed as a basis for subsequent decisions in treatment.

2. In the main it can be assumed that all missiles maintain a straight course through soft tissues. Bony structures may deflect a missile, but it is surprising how frequently the fragment passes directly through bone, maintaining its course unaltered. When velocity is completely lost, the fragment may come to rest at the most dependent portion of a serous cavity. It has not been our experience to find the course of any missile appreciably altered by varying densities of soft tissue structures, though lesions in widely separated portions of the small intestine or apparently bizarre courses through the body may make it appear that they have been deflected. Changes in the position of the viscera and the attitude of the patient's body at the time of wounding have always afforded complete explanation in these instances. Localization of the missile by roentgenograms in two planes or reconstruction of the track between wounds of entrance and exit is the most important diagnostic feature. The necessity for locating any missile that has produced a wound between the shoulders and the knees cannot be too strongly stressed. Any such missile may have entered the peritoneum.

3. In the main the signs of peritoneal irritation are reliable. Profound shock, morphinization, confusion and stupor arising from intracranial blast may depress these signs markedly. The occasional case occurs in which rigidity is slight or absent on admission with the patient in severe shock, but as the shock picture improves the abdomen becomes markedly rigid. Tenderness is likewise variable and ill co-ordinated with the amount and type of spillage. A most valuable sign has been the presence of audible peristalsis with the stethoscope. We have not seen a single case of perforation of a hollow viscus into the free peritoneal cavity in which peristalsis could be heard. Absence of peristalsis is, in contrast, not a reliable indication that hollow viscus perforation is present. Free blood in the peritoneum, retroperitoneal hematoma, severe contusion or blast injury may stop peristalsis completely. But in the summation of diagnostic considerations the presence of peristalsis may swing the decision against surgical invasion of the peritoneum.

4. There remain cases in which it is very difficult definitely to rule out involvement of intraperitoneal structures. We have felt that the policy of surgically exploring the abdomen when reasonable doubt remained was wise. An analysis of 50 so called "negative bellies" by the senior author failed to encounter a single case in which exploration was responsible for the death of the patient. On the other hand, exploration certainly contributes to morbidity and should not be taken lightly. In this series of cases celiotomy has been performed on only 1 occasion without finding perforation of hollow viscus or involvement of solid viscus, and in this patient the lesion was confined to the region behind the right colon producing a contusion of the colonic wall which was not exteriorized and which did not subsequently perforate. With thorough diagnostic consideration negative exploration should become less frequently necessary as the experience of any given surgeon increases with this type of injury.

SHOCK THERAPY

The degrees of shock exhibited by these patients at the time of admission are indicated in Table III together with the mortality rates for the different arbitrarily selected groups. The seriousness of the shock picture is the most reliable prognostic sign. In those cases not exhibiting clinical shock mortality is less than 10 per cent, while in those in pro-

TABLE III.—SHOCK IN RELATION TO MORTALITY—125 CASES

Degree of shock	Number	Lived	Died	Per cent mortality
None*	57	51	6	10.5
Moderate	35	24	11	31.4
Severe	33	13	20	60.6

*None, no apparent shock, blood pressure above 110, pulse below 100. Moderate, blood pressure below 110, pulse above 100, objective signs of shock present.
Severe, blood pressure below 70, pulse above 120, objective signs of shock present.

found shock mortality is more than 60 per cent.

It is not within the scope of this paper to discuss the complex and still ill understood phenomena of shock. But there are certain features that have impressed us and are worthy of mention:

1. A clinical picture impossible to differentiate from shock is produced by severe contamination of the peritoneum with the content of colon or distal ileum. There are few cases in which blood loss has not also been a factor. Frequently, however, the degree of shock exhibited is out of all proportion to blood loss, and in most of these cases contamination with colon organisms has been a prominent feature. Burbank has taken hematocrit readings on some of these cases and has found a significant hemoconcentration when blood loss was not marked, near normal hematocrit readings when hemorrhage was combined with contamination in the production of the shock picture, hemodilution when hemorrhage has been the major or sole etiologic factor. We have not, as yet, had sufficient opportunity to confirm these findings, but they may be of considerable importance in determining the relative amounts of blood and plasma that are optimum in the treatment of a given patient. A constant observation has been that in those patients in whom contamination is the major or the sole cause for shock, response to replacement therapy is usually slow or nonexistent. In these patients the prognosis is very grave.

2. When there is relatively little spillage of colon content, when the perforations are entirely confined to the upper intestinal tract, or the lesions are chiefly or entirely of solid viscera, shock is relatively proportionate to blood loss. Unsplinted fractures of major long bones or disturbances in cardiopulmonary physiology due to associated chest wounds or to "blast" may disturb this proportionate relationship. It must also be kept in mind that it is possible physiologically to compensate for loss of upwards of a liter of blood from the circulation, especially if this loss occurs slowly. The additional loss of relatively small quantities of blood may rapidly induce a state of profound shock. It is well to keep this in mind when considering the replacement of blood loss, for the patient faces in every case additional blood loss inevitably associated with major surgery which may prove rapidly fatal if difficulty is encountered in controlling bleeding from a major vessel.

3. Fatal peritonitis has been rare except in those cases in which contamination has not been a major factor in the production of shock. From 1 to 3 hours spent in treating shock is well spent as long as there is continued improvement. The working rule on which we have tried to proceed is as follows: Rapid infusion of whole blood and plasma is begun as soon as possible. An attempt is made to estimate tentatively the probable amounts of blood lost. After an adequate replacement of blood and plasma loss, in an hour to an hour and a half's time, if there is little or no response to shock therapy, there must be active causative factors responsible. In the main there are four such mechanisms, most of them amenable to surgery: (a) continued hemorrhage, usually concealed; (b) severe fecal contamination of the peritoneum; (c) disturbance of the cardiorespiratory mechanism from thoracic injury; (d) early, fulminating anaerobic infection with gas-forming organisms. "Blast" injury to viscera and massive evisceration less frequently prevent response. If there is no response to shock therapy, or if response has begun but is interrupted and the patient's condition begins to deteriorate, operation is begun without delay.

The opinion that massive transfusion of whole blood is essential to the adequate resuscitation of shocked patients cannot be escaped. Plasma has frequently been given in installations first receiving the patient, but is used by us as the initial fluid for replacement

TABLE IV.—AVERAGE VOLUMES OF BLOOD AND PLASMA USED—31 CASES OF SEVERE SHOCK

	Amount c.c.	No. Units
Blood per case*	2800	5.5
Plasma per case	770	3.09

*Representing the blood from 176 donors, plasma from 96 donors, an average of 8.8 donors per case.

while banked blood is being cross-matched. The amounts of blood used in 31 cases of severe shock may be seen from Table IV, an average of 2800 cubic centimeters for all cases in which accurate records are available[1]. Early in our experience in using blood in these unprecedented amounts we became convinced that it was relatively easy to overload these patients with isocolloidal solutions, leading to overloading of the right heart, elevated venous pressure, and the clinical picture of right heart failure. The following case is illustrative:

CASE 1. An American soldier, aged 24 years, was admitted in mild shock following a wound by a rifle bullet that perforated the right anterior chest in the fourth interspace. The missile could be felt beneath the left costal margins above the 11th rib's tip. Signs of peritoneal irritation were present and there was blood in the gastric washings. He had received 2 units of plasma just prior to admission and after 1000 cubic centimeters of blood operation was begun. The right thorax was opened by extending the wound of entrance. The missile had passed through the anterior margins of the middle and lower lobes of the right lung, lacerated the pericardium and the diaphragmatic pericardium entering the left lobe of the liver. The heart was not damaged. Free hepatic fragments were removed from the pericardial cavity and the diaphragm and pericardium closed. Celiotomy was performed through a left paramedian incision. The missile had passed cleanly through the left lobe of the liver and caused a tangential wound of the greater curvature of the stomach which was closed. The lower pole of the spleen showed a tiny laceration that was not bleeding. Splenectomy was not performed. The missile was removed through a counter incision and drains passed to the superior and inferior surfaces of the liver brought out through this wound. He received 500 cubic centimeters of blood and 1 unit of plasma during operation and another 500 cubic centimeters of whole blood immediately thereafter.

After two stormy postoperative days marked by mental confusion, high fever, rapid pulse, and vascular instability, on the morning of the third day there was severe pulmonary edema, thin, frothy fluid pouring from the mouth, severe dyspnea, coma, thready, almost imperceptible pulse. The peripheral veins were markedly dilated, especially the neck veins. Phlebotomy was performed, 600 cubic centimeters of blood being removed. Recovery was dramatic. Within an hour the chest was entirely dry, blood pressure normal, pulse full and regular though still rapid. The signs of intracranial injury gradually decreased. Patient was evacuated on the 10th postoperative day and transported to a general hospital without further incident.

[1]This includes all replacement therapy used in resuscitation from the time of wounding, through the operation, and the immediate postoperative period.

The clinical evidences of increased venous pressure have not often been as clear cut as in this case. Another instance wherein phlebotomy might have rapidly improved the patient is detailed in Case 9. We now believe that the patient who fails to respond completely to the preoperative administration of 1500 cubic centimeters of blood will not profit by further administration and operation should be undertaken without delay.

Regardless of the shock state, operation is not begun without a cannula in a vein and blood or plasma running in. Improvised sternal needles for marrow infusion have been constructed by Army Ordnance and have proved especially valuable when collapse of veins has made cannulization difficult and the flow of fluid agonizingly slow. Resuscitation is continued throughout the operation. No patient died during anesthesia, nor has it been necessary to curtail operative procedures or to adopt compromise procedures in deference to the precarious condition of the patient. It is frequently the case, especially when there is continued bleeding from large vessels, that the patient leaves the table with function restored in better condition than at the start of the operation.

ANESTHESIA

Ether has been selected as the anesthetic agent in every case. Since these patients have not received the preparation of abstinence from eating and morphinization usual to elective surgery, as thorough as possible gavage of the stomach has been done routinely. Additional preoperative morphine has rarely been necessary, being usually given in amounts bordering on excess prior to admission. Atropine, 1/100 grain has been given routinely intravenously shortly before induction. The endotracheal tube has been

routinely introduced to aid in the maintenance of an adequate airway and to administer positive pressure anesthesia when necessary if the pleura were opened. The relaxation achieved has left nothing to be desired from the surgeon's standpoint. Oxygen tension has been maintained at high levels throughout, an exceptionally important consideration in patients recovering from severely shocked states. Particular attention has been paid to the removal of accumulated intrabronchial secretions of blood and mucus at the close of the procedure. It has usually been accomplished by means of a catheter introduced through the endotracheal tube, but in the occasional case wherein this method has not achieved a dry tracheobronchial tree suction has been applied under direct vision through the bronchoscope while still under anesthesia. This procedure has resulted in steady decrease in the frequency of postoperative atelectasis and pneumonitis.

OPERATIVE TREATMENT

Proved, sound surgical principles nowhere find greater application than in the complex technical problems customarily encountered in the treatment of abdominal wounds. We have found certain procedures particularly applicable to this problem.

Immediately following his admission, all clothing is removed and each patient is placed on a freshly dressed litter on which he remains for x-ray examination, shock therapy, throughout the operation, and frequently for the first few hours in the postoperative tent until resuscitation treatment is complete. We prefer to leave him on this litter during the operation for greater ease in handling, the litter usually swung between improvised saw horses. The placement of a rolled blanket under the patient in the lateral recumbent position takes the place of "breaking" the table when a flank or lower thoracic incision is made. When pathology is anticipated deep in the pelvis a thickly folded blanket accomplishes Trendelenburg position very satisfactorily. The usual operating room régime is otherwise used, full masking of all personnel, gowns, gloves, and complete sterile draping. We prefer to perform débridement of wounds of the back and buttocks prior to entering the abdomen. Turning the patient to perform such procedures subsequent to celiotomy may induce a severe fall in blood pressure.

Selection of the incision is made to conform to the expected pathology. The most usual incision is, of course, the vertical rectus type, allowing extension upward or downward to procure the widest possible exposure of the entire peritoneal cavity. We have used the paramedian, rectus retracting type most frequently feeling that it allowed the strongest possible closure. In attacking the splenic area from below, this incision has been extended through the left rectus and obliques in "T" fashion. In lesions confined to either of the upper abdominal quadrants, with entrance or exit wounds in the flank, especially with indication of severe renal pathology, a transverse flank type of incision has been preferred. This incision has afforded excellent exposure of the renal areas and the splenic and hepatic flexures in particular and allows complete exploration of the small bowel, and the entire abdomen with the exception of the attached colon of the opposite side. It has one serious fault in that, if exteriorization of the colon is necessary it is difficult to find sufficient space on the abdominal wall to bring it out through a separate stab wound without tension. In large, tearing wounds of the abdominal wall with a ragged subcutaneous track the peritoneum may be opened along the direction of the missile following débridement of the wound.

For the past year cotton suture material (No. 40 sewing cotton) has been routinely used. It was selected without previous personal civilian experience because of the difficulties in procuring silk of sufficiently fine caliber, and has proved to be most satisfactory.

Early in our experience the necessity became apparent for securing closure of the abdominal wall as strongly as possible. In the first 28 cases there were 6 wound dehiscences, induced by coughing, nutritional deficiencies, and the inevitable delay in healing in the grossly contaminated wound. Although it has certain objections, steel wire was adopted routinely as a tension suture.

Except in certain desperate cases the wound was closed in layers; continuous fine catgut was used in the peritoneum, interrupted cotton sutures in the posterior and anterior rectus sheaths. The skin was not closed in any case with perforation of a hollow viscus, as it is our opinion that in most instances wound sepsis originates in the subcutaneous areolar tissue. Coarse mesh vaseline gauze was laid beneath the wire sutures to keep the skin margins apart during the first few postoperative days. A request has been made that these wire sutures be left in place 21 days. No attempt has been made to wall off the operative incision from the exteriorized colon. If there were no hollow viscus perforation, the skin margins were approximated with interrupted cotton sutures widely placed. The results have been most satisfactory. There have been no wound dehiscences in the subsequent 100 patients. Cosmetic results have not been optimum, but it has not been necessary secondarily to close the superficial wound.

In exploring the peritoneal cavity, an attempt is made to retrace the course of the missile. Radical shifts in position of viscera, particularly small bowel, that may occur subsequent to passage of the missile through the peritoneal cavity should be kept constantly in mind. The blood in the peritoneum is removed by suction and the large clots frequently present both manually and by scooping them out with laparotomy packs. No attempt is made to remove the blood completely, because we believe that such a maneuver is manifestly futile and that the blood left acts as an autotransfusion no matter how severely contaminated. If there has been severe hemorrhage rapid search is made for its source and the bleeding vessels ligated or otherwise temporarily controlled. Any apparent gross perforation of the colon is isolated as completely as possible in order to minimize contamination. If small bowel perforation is likely, the entire intestine is systematically explored from proximal jejunum to terminal ileum, or vice versa, each perforation is tagged with an Allis's forceps and careful count is kept. Finding of an "odd" number of perforations must be explained. Careful search is made for perforation concealed between the leaves of the mesentery which are likely to be overlooked and are troublesome to close. Particular attention must be paid to the retroperitoneal surfaces of the viscera fused to the posterior parietes. The ascending and descending colons are mobilized and their posterior surfaces inspected if perforation from behind is at all likely. In the same way the duodenum is mobilized by lateral incision and retracted medially to expose its posterior surface. The posterior surface of the stomach is exposed through the avascular gastrocolic omentum or through the transverse mesocolon. The most likely areas for overlooking perforations are thereby exposed. The 2 following cases are illustrative:

CASE 2. An American soldier, aged 27 years, was admitted 6 hours after sustaining a wound by a mortar fragment that entered the left 10th interspace in the anterior axillary line; the fragments were palpable posteriorly above the crest of the left ilium. The missile had passed through the diaphragm below the pleural reflection, perforated the splenic flexure and entered the retroperitoneal tissues above the left kidney. An anterior perforation was closed, after great difficulty was encountered in exposing and mobilizing the splenic flexure. Proximal defunctioning transverse colostomy was performed. The patient died on the 9th postoperative day following a stormy septic course. At autopsy there was found a small perforation on the posterior aspect of the descending colon which had not been closed and drainage from which was responsible for a tremendous phlegmon of the perirenal tissues and the tissues of flank and lower chest.

The extension of this incision through the left rectus and obliques in order better to expose the splenic flexure would have allowed of its complete mobilization and exteriorization.

CASE 3. A German prisoner, aged 21 years, was admitted 8 hours after being wounded by a rifle bullet which entered at the tip of the left 11th rib. He was not in shock but all signs of peritonitis were present. There was a single complete transection of the upper jejunum with severe peritonitis. The missile had perforated the mesentery of the mid-descending colon, "contusing the colon," and passed posteriorly to exit in the left flank. After débridement the jejunal continuity was restored by end-to-end anastamosis. The colon was not treated. For the first day the convalescence was satisfactory, then fulminating sepsis developed with death on the 3rd postoperative day. At necropsy there was generalized foul, fibrinopurulent peritonitis with a

perforation of the portion of the descending colon between the mesenteric leaves.

Whether a small perforation of the colon was missed or whether there was subsequent sloughing of the colonic wall in the area of contusion is not definite. In any case there was an error in judgment. The descending colon should have been exteriorized.

Except for conduction of secretions of liver, kidney, and pancreas to the outside, no attempt has been made to drain the peritoneal cavity.

That the incidence of involvement of the various viscera is roughly proportionate to their displacement is borne out in Table V. Complex injuries to numerous viscera is the rule, and the contribution to mortality made by each defies statistical analysis.

TABLE V.—INCIDENCE OF INVOLVEMENT OF THE VARIOUS ORGANS—130 PATIENTS

Stomach	20	Pancreas	2
Duodenum	6	Adrenal	2
Small intestine	55	Bladder	5
Colon	57	Ureter	1
Rectum	9	Urethra	1
Liver	34	Diaphragm	33
Gall bladder	3	Appendix	1
Spleen	14	Vena cava	3
Kidney	24		

Hollow viscera. Perforation of a hollow viscus was found in 99 cases with a mortality of 38 per cent (Table VI). The tearing action of high explosive fragments tends to produce large lacerations from which spillage of intestinal content is great. The contractile action of the bowel tending to close small perforations minimizes the amount of spillage, which in lesions less than 1 centimeter in diameter is usually very slight.

Except for the technical difficulties of approach to the gastric fundus, especially on its posterior surface, perforations of the stomach have proved to be relatively benign. Since high gastric lesions are frequently associated with thoracic involvement we have preferred whenever possible to approach them through the chest.

The survival rate of patients with lesions of the duodenum is very low, not so much apparently because of factors intrinsic in the duodenum, but because of its location near great vessels, the pancreas, the biliary tree, stomach, and colon which tends to make for a very complex situation. Duodenal closure, even of large lacerations on the posterior nonperitonized surface has given little difficulty. None of these closures has subsequently leaked to produce duodenal fistula.

There has always existed among military surgeons firm prejudice against resection of small intestine, founded on previous experience that few survived. Although in complete agreement that simple closure is always to be preferred to resection we have encountered no difficulties with resection per se. We have preferred end-to-end anastomosis chiefly because it has been more rapidly and simply accomplished. With the peritoneum already contaminated, closed "aseptic" anastomosis has seemed an unnecessary refinement, especially since no clamps have been available that met ideal standards of length and narrowness of blades. An open, two layer anastomosis has been made in each case, by use of nonabsorbable sutures in the seromuscular layers, and removal of a greater portion of the bowel at the antimesenteric border in order to achieve a lumen of greater size. Great care has always been taken that the blood supply of the suture line be adequate. In spite of the fact that all these anastomoses were made in the presence of already established peritonitis, none has leaked. Nor has intestinal obstruction developed at the anastomotic site. Patients in whom intestinal resection is necessary will inevitably succumb in higher percentage than those handled by simple closure, but it is our impression that this is in very great part due to the greater complexity of the pathology. When several large linear lacerations and transections have occurred in a short segment of bowel, it has seemed safer to resect the involved segment and to make a single anastomosis than to attempt plastic closure of these several tears. Linear tears are closed in transverse direction, but great care must be taken that distortion does not make for likely intestinal obstruction later on. Intestinal obstruction, varying in degree, has been a frequent late complication, from plastic peritonitis with volvulus in most cases, the sites of obstruction bearing less relationship to

the areas where perforations were closed or anastomoses made than to the areas where serosal abrasions have occurred and where the bowel has been handled a great deal during the manipulations of repair.

Colon. Contamination of the peritoneum by colon content is the single most lethal factor producing death in abdominal wounds (Table VI).

TABLE VI.—RELATIONSHIP OF CONTAMINATION OF PERITONEUM TO MORTALITY

	Cases	Died	Per cent Mortality
No intraperitoneal perforation of hollow viscus	32	0	0
All intraperitoneal perforations	99	38	38
Stomach and small bowel perforations only	42	12	29
Colon perforation	57	26	44

The principle of exteriorization of lacerations of colon is particularly adaptable to the lesions of the colon produced by high explosive and high velocity missiles. Even the smallest perforation of the colon is usually surrounded by an area of ecchymosis which, when observed in the exteriorized loop, invariably undergoes necrosis and sloughs to the very margin of the ecchymotic area. The difficulties of estimation of the extent of this necrosis make simple closure of these lacerations hazardous. In addition, exteriorization accomplishes decompression. There are certain situations, however, in which the exteriorization principles are inapplicable or unsatisfactory. These are particularly peculiar to the right colon, large lacerations of which are likely to be accompanied by high mortality because of the liquid character of the colonic content which flows readily into the peritoneal cavity carrying with it a great concentration of organisms which are rapidly disseminated throughout the peritoneum. Exteriorization, with the suturing of ileum to the remaining distal loop of colon is particularly difficult to handle in the patient facing a long trip through the chain of evacuation. The maintenance of water and electrolyte balance and the frequent dressings of the wound necessary to avoid serious erosion of skin in the presence of ileal fistula make these patients poor candidates for transportation. On the other hand, the patients with small perforations, particularly of the cecum and proximal ascending colon have done very well following the conversion of these wounds into a cecostomy, by suturing the colonic wall about a one inch rubber tube and securing it to the deep fascia by several interrupted sutures. When small through-and-through wounds have been encountered the posterior wound has frequently been closed and the anterior wound converted into a cecostomy in this fashion. The cecostomy tube is usually removed between the 4th and 6th postoperative days and drainage has ceased a very few days later. By complete mobilization of the right colon and the hepatic flexure, exteriorization with the suturing of an adequate spur can usually be accomplished in the distal half of the ascending colon. In those long, linear tears, especially in the proximal half of the ascending colon, the most satisfactory answer seems to be resection of the proximal portion to beyond the tear, ileotransverse colostomy (which we prefer to do in end-to-side fashion) bringing the proximal hepatic flexure or transverse colon out through a stab wound.

Perforations and lacerations of the remaining colon are exteriorized through a short muscle splitting incision as far away from the primary incision and the wounds produced by the missile as is consistent with the avoidance of tension on the bowel. To this end also, attached portions of the colon are liberally mobilized. A spur, ideally from 5 to 6 inches in length, is constructed by the simple expedient of turning the bowel toward the center axis of the body, suturing the two teniae liberae together with a single running stitch of catgut. Portions of the transverse colon used in making this spur are denuded of their omental attachments. The colostomy thus constructed is opened immediately following operation.

The retroperitoneal tissues exposed to extensive contamination by the mobilization of attached colon have been a frequent source of infection, in fact, the most frequent situation for the development of abscess next to the subphrenic areas. The retrocolonic areas therefore are always drained, usually through the flank wound which already exists and is enlarged by débridement.

The principle of proximal decompression and defunctioning is applied routinely to lesions of the distal sigmoid and rectum. Perforations of that portion of the sigmoid and rectosigmoid that will not allow exteriorization are closed, and, if the rent extends below the pelvic floor into the rectum, the suture line is excluded from the peritoneum by transposing the pelvic peritoneum proximal to it. The proximal colostomy in cases of this sort, and when large lacerations are present in the rectum is constructed likewise with a spur and completely cut across to allow for complete defunctioning. When there is a small lesion of the rectum wherein complete defunctioning seems less important, a simple loop colostomy has been performed.

No attempt has been made to suture lacerations of the rectum since early experience demonstrated that these suture lines do not hold. In fact, additional rectal wall may be sacrificed by its inclusion in the suture. Adequate drainage of the pararectal fascial spaces is secured, following which the rectal wall heals itself. The blunt dissection of the rectum from its loose sacral attachments is not considered complete until the sacral promontory is felt beneath the dissecting finger. We have preferred a hockey-stick incision with its vertical arm on the side of greatest involvement. Since Colcock has reported osteomyelitis and pain on pressure as late complications from resection of the coccyx, we have avoided it except in 1 patient whose distal sacral segment and coccyx were fractured by the passage of the missile. After division of the fascia propria and blunt dissection of the rectum away from its areolar attachments to sacrum, soft rubber drains are passed up to or above the level of the perforation. Thorough débridement of the buttock wounds is carried out. Anaerobic sepsis, so likely in the gluteal muscles, has not been encountered as a postoperative complication.

Liver. Fracture of liver substance has been encountered more frequently than the simple "drill holes" of the liver produced by small caliber small arms fire of low velocity. In certain cases these liver fractures have been very extensive, segments of lateral margins torn away, ragged V-shaped segments removed from one or the other lobe, and in 2 cases tremendous fissures extending more than two-thirds through the substance of the hepatic body. But in none of these cases has there been sufficient bleeding to warrant packing to control hemorrhage. Moderate oozing is occasionally encountered, which has invariably been controlled by placing a warm sponge against the oozing surface during the subsequent manipulations, very rarely requiring the aid of a piece of crushed muscle taken from the abdominal wall. Liver packs have proved a nidus of infection, sinus formation, and have often required anesthesia for removal. Secondary hemorrhage has in certain cases followed their removal. It has also seemed to us that the presence of a pack might jeopardize the blood supply of that portion of the hepatic lobe distal to the laceration from the hilum. Regardless of the size of the lesion, the most important consideration has been to conduct the bile to the outside. Observation of cases in base installations has impressed us with the amounts of bile that drain from liver wounds and the lengths of time the drainage may continue. One case was observed in which bile was still draining 73 days following the initial operation from a moderate sized fracture of the liver. Accumulations of bile in the peritoneal cavity producing chemical peritonitis make for a serious postoperative complication which in certain cases may become a lethal combination with other wounds. It has seemed important enough to provide a vent to this bile, that we have been constrained to operate upon all patients with liver injury except when the missile was extremely minute (1 case previously alluded to). This consideration is also important in the handling of wounds of the liver produced through the right diaphragm, more thoroughly discussed under the heading of thoracoabdominal wounds, in which the subphrenic and subhepatic spaces are routinely drained. In summary it may be said that the *sine qua non* of the treatment of liver wounds is drainage.

Metallic foreign bodies imbedded in liver tissue are remarkably well handled without respect to their size. No attempt is made to

remove them at the initial operation unless they are readily available, protruding from the liver surface.

Spleen. The "gunshot" wounds of the spleen have exhibited one striking feature different from the usual experience with closed traumatic rupture of the spleen: unless there is a wound of the great vessels near the hilum of the spleen they do not continue to bleed. No satisfactory explanation for this alteration in the usual pattern presents itself. Extensive laceration, even fragmentation of the spleen with free portions herniated into the thorax or free in the peritoneal cavity have been a frequent finding. There is usually considerable free blood in the peritoneal cavity, but the spleen itself as encountered at operation is either not bleeding at all or gently oozing. Shock is no more frequent in splenic injuries than in injuries of other abdominal viscera. The following case is typical:

CASE 4. An American soldier, aged 24 years, was admitted 5½ hours after sustaining a wound over the left 11th rib in the anterior axillary line by a mortar fragment. Two units of plasma were given prior to admission. He was not in shock, blood pressure 110/80, pulse 100. The abdomen was boardlike. Stomach contents and urine were negative. At operation the abdomen contained an estimated 1000 cubic centimeters of liquid and clotted blood. There was a "tremendous laceration of the lower half of the spleen, with a great deal of surrounding ecchymosis of the ligaments of the spleen," but no active bleeding. The diaphragmatic origin was torn below the pleural reflection. Splenectomy was performed and the diaphragm repaired. Except for transient atelectasis of the left lower pulmonary lobe he made an uninterrupted convalescence and was returned to full duty on the 25th postoperative day.

In considering civilian experience in the frequency of secondary hemorrhage following rupture of the spleen, we have performed splenectomy for all but the most extremely minor lacerations. The only such case in which it was felt that the slightly fractured spleen could be safely left in had no further difficulty with the spleen during the short period we were able to follow his progress. Splenectomy in cases in which the spleen was the sole abdominal viscus damaged has not resulted in death or severe complication in a single case (Table VII). The transthoracic approach has delighted us in the ease with

TABLE VII.—MORTALITY FROM SPLENECTOMY —14 CASES

	Cases	Deaths	Mortality per cent
Transphrenic	9	0	0
From below	5	4*	80
Total	14	4	28

*These 4 deaths were due to extensive contamination of peritoneum and pleura by hollow viscus content.

which splenectomy may be performed. If there were no penetration of the pleura, or if the peritoneal pathology were not approachable through the diaphragm, the transverse subcostal approach has been used whenever practicable. This series includes 2 patients who have returned to combat duty within 6 weeks after splenectomy.

Kidney, ureter, and bladder. Wounds of the kidney have been seen in 24 patients. In cases with extensive extravasation of blood about the kidney, sufficient dissection was carried out to visualize the kidney. As with liver and spleen, the renal parenchymal substance has not continued to bleed, except for moderate oozing, unless the wound were near the hilum involving the major blood supply. Even though there were extensive fractures through the renal substance, with portions of the kidney torn completely away and a major calyx involved, the treatment has been conservative. Adequate drainage has been established to conduct the urine to the outside. Drainage of urine in these patients has continued for a very long time. Microscopic blood and sterile pyuria have required weeks to disappear. Plastic reconstruction of the kidney by débridement and suture has not seemed indicated. The following case is illustrative of the tremendous powers of healing of the conservatively treated kidney:

CASE 5. A Japanese-American soldier, aged 27 years, sustained a perforating wound from an artillery fragment that passed through the right flank. He was admitted 9½ hours later in severe shock which responded promptly to the administration of 1000 cubic centimeters of plasma and 500 cubic centimeters of whole blood. The missile had torn the lateral 3 centimeters of the right lobe of the liver away, almost completely transected the mid-ascending colon, and carried away the lower third of the right kidney into the lower major calyx. Neither liver nor kidney was bleeding. The torn colon was exteriorized, and the hepatic and renal areas drained through the large débrided posterior wound. Except

for a low grade fever, early convalescence was smooth. Urine and bile drained in large amounts through the posterior wound. Six weeks later he was seen at the general hospital in the base, still draining bile stained material in small amounts from the small posterior sinus, otherwise in excellent general condition. Retrograde pyelograms at this time were normal except for very slight distortion of the inferior major calyx. He stated in a letter almost a year later that he was on limited duty status in a rearward area "feeling fine."

Nephrectomy has been performed in 6 instances (25 per cent), in each case because of severe intractable bleeding.

Only 1 lesion of the ureter has been encountered in our personal experience, in this case associated with severe damage to the kidney to which the only answer was nephrectomy. We know of no case in which there has been sufficiently slight damage to the ureter to permit of successful plastic repair.

Perforations and lacerations of the bladder have been closed. In certain instances, especially when the missile has passed through the floor of the bladder or its anterior wall the dissection in the prevesical spaces has been extensive and the repair difficult. A suprapubic cystostomy tube has been sutured in place for urinary drainage. In many instances indwelling urethral catheter drainage might have sufficed, but the difficulties of maintaining the catheter in place during transportation have made cystostomy the more desirable procedure.

Great vessels. The initial attitude toward the problem of retroperitoneal hematoma was conservative, in accordance with the accepted attitude toward the retroperitoneal hematomas of crushing injury of civilian experience. Unless there was continued bleeding, the hematoma was left severely alone. An early unfortunate experience (Case 6) which has been repeated in the experience of others has made us more vigorous in exploring these hematomas and in ligating large bleeding vessels, more to avoid the late complication of suppurative thrombophlebitis with fatal septic infarction of lung than to avoid secondary hemorrhage. This has seemed particularly indicated in instances in which the retroperitoneal hematoma communicates through the missile track with the contaminated peritoneum, and especially when the missile has passed through the colon in its course toward the posterior parietes. This attitude has seemed profitable.

CASE 6. An American soldier, aged 21 years, was admitted 6 hours after fragments from an aerial bomb had caused superficial wounds of the right arm and a penetrating wound of the mid-epigastrium. The small missile had passed through the mid-transverse colon, produced numerous rents and perforations in a segment of ileum a foot from the ileocecal juncture, and passed into the retroperitoneal tissues to the left of the midline about 3 centimeters above the origin of the inferior vena cava. The large retroperitoneal hematoma was not increasing in size. There was severe contamination of the peritoneum and the intraperitoneal blood. Resection of a segment of the small bowel with end-to-end anastomosis, the transverse colon exteriorized, the retroperitoneal hematoma not disturbed. For the first 9 days convalescence was satisfactory except for a low grade fever, which was first thought to be due to malaria when parasites were found on examination of the blood. At the evacuation hospital he developed an abscess about the posteriorly placed missile lateral to the vertebral bodies which had not been removed. Following the drainage of this abscess he developed severe ileus, high fever, jaundice with marked enlargement of the liver. Death on the 47th postoperative day from a suppurative thrombophlebitis of both femoral veins and inferior vena cava with multiple septic infarcts to lungs and liver.

Exploration of the retroperitoneal tissues might have required ligature of the inferior vena cava, but the removal of the missile and avoidance of the subsequent abscess would probably have saved the patient.

We know of no patient with an aortic wound who has survived to reach the operating table, although 2 patients with aortic wounds have succumbed shortly after their admission to our hospital. Lesions of almost every other great vessel have been encountered. Associated with wounds of large vessels is a particular syndrome which it may be well to describe. If the patient has been in severe shock on admission he may make an excellent response to replacement therapy up to a certain point, attaining a blood pressure of perhaps 90 systolic. Or the shock picture may have been slight and response to shock therapy prompt. Immediately, however, upon the opening of the peritoneum the blood pressure drops to zero with the release of the hydro-

a b

Fig. 1. Case 7. Left thoracoabdominal wound. a, Preoperative vertical roentgenogram of the chest showing stomach herniated through the large rent in the diaphragm, fractured spleen above and medial to the stomach, slight hemopneumothorax. b, Vertical roentgenogram of the chest 36 hours after thoracotomy showing complete reexpansion of the lung, the stomach reduced, the diaphragm repaired.

static pressure of the collected blood within the peritoneum sustained by the pressure of the abdominal musculature. After ligature of the vessel there is usually prompt recovery from the hypotension. Distention of the abdomen with blood with slow or no response to replacement therapy is a most ominous sign and usually results from a rent in an artery of large caliber. Collected experience has indicated that the great veins may be ligated with impunity, including the inferior vena cava up to the level of the renal veins.

THORACOABDOMINAL LESIONS

For purposes of this discussion thoracoabdominal lesions are limited to those in which the missile has passed through both pleura and diaphragm. Combined thoracic and abdominal cases in which there is associated injury to the chest by one or more other fragments are excluded, as are those perforations of the diaphragm beneath the pleural reflection. There were 31 thoracoabdominal injuries in this series, an incidence of 24 per cent. The mortality of this group was 19 per cent, slightly lower than the general mortality of the entire series.

Thoracoabdominal lesions form the most frequent indication for major surgical invasion of the thoracic cavity by "definitive thoracotomy." It is beyond the scope of this discussion to consider the indications for definitive thoracotomy in detail. Our present attitude may be summed up as follows: The repair of the diaphragm is much more readily accomplished from above, and the repair achieved is likely to be much more secure. If there is a sucking wound or extensive dam-

age to the thoracic wall, especially when the thoracic wound is below the 7th interspace affording satisfactory exposure of the diaphragm by extending the incision necessary to débridement of the wound, the diaphragm is repaired from above. This approach is especially appropriate if the pathological condition likely to be encountered can be entirely repaired through an extension of the wound in the diaphragm. We have been gratified to find how readily subphrenic organs are approached by the transphrenic route. As has been previously stated, the removal of the spleen is much more readily accomplished from above than from below, and the same is obviously true of the approach to the gastric cardia and fundus and the entire posterior surface of the stomach. Nephrectomy can be accomplished readily through a low thoracic approach either on the right or the left. The splenic flexure of the colon is readily mobilized and exteriorized through a subcostal stab wound if perforated. The small intestine may be explored through the left diaphragm down to the distal reaches of the ileum.

Although there has been general agreement about the necessity for closure of the left diaphragm to prevent subsequent herniation, we are of the opinion that it is just as important to close the right diaphragm, if there is a lesion of any size in it, to prevent the drainage of bile into the pleura from the liver wound which is almost inveriably associated with lesions of the right diaphragm. Continued flow of bile into the pleura produces an intense chemical pleuritis causing transudation of a great deal of fluid into the pleura requiring aspiration for a very long time. Total empyema is likely to result. The objection that the presence of the liver precludes exploration of the subhepatic areas has not proved a valid deterrent. Nephrectomy has been accomplished through the right diaphragm as readily as through the left. The liver may be retracted to the left, thus exposing the gall bladder, the hepatic flexure and proximal transverse colon, the duodenum and biliary tree.

The frequency with which the abdominal and the thoracic approach has been selected is shown in Table VIII. In those cases in which both thoractomy and celiotomy must be done, we have preferred to do the chest work first in order to restore the pulmonary physiology to as nearly normal as possible before proceeding to the more shocking celiotomy.

TABLE VIII.—THORACOABDOMINAL WOUNDS—ROUTE OF APPROACH—31 CASES

Route of approach	Cases	Died	Mortality per cent
Thoracotomy alone	21	2	10
Celiotomy alone	4	2	50
Thoracotomy plus celiotomy	5	2	40
Not operated	1	0	
Total	31	6	19

The phrenic nerve has been crushed whenever it seemed desirable to achieve phrenic paralysis to quiet the diaphragm and to favor its healing. This fact has seemed particularly indicated when there was an extensive wound of the diaphragm, especially in those cases in which the diaphragm was avulsed near its origins for a considerable distance. Phrenic repair has usually been accomplished in two layers by overlapping the leaves of the diaphragm a centimeter and securing the closure with interrupted mattress sutures throughout. Every effort has been made to achieve rapid, complete re-expansion of the lung following surgery. The most successful plan has been to institute water-trap drainage of the chest through two tubes, an upper one in the anterior 2nd interspace, another in the posterior axillary line, usually in the 7th interspace. The lung has been re-expanded under positive pressure by the anesthetist prior to completing the last sutures in the thoracotomy closure. The tubes have been removed after they have ceased to function when the lung has come out against them, usually in 48 hours. In many instances the chest has remained completely dry (Case 7), although frequently from 1 to 4 daily aspirations have been necessary. Aspirations are continued until less than 50 cubic centimeters are obtained.

CASE 7. An American soldier, aged 21 years, was admitted 4½ hours after sustaining wounds of both chests from artillery fire, not in shock, with blood pressure of 130/70, pulse of 120. The missile had entered the right posterior chest over the 10th rib

just medial to the posterior axillary line and exited through the left chest fracturing the 8th and 9th ribs. This wound was sucking markedly. There was a small amount of blood in the gastric washings. The x-ray film (Fig. 1a) showed the stomach herniated through the left diaphragm into the left thorax. Thoracotomy was performed by excising an additional length of the 9th rib. The fractured spleen was herniated with the intact stomach through a large rent in the diaphragm and there were several free fragments of spleen, comprising about half the spleen, in the pleural cavity. The remaining spleen was not actively bleeding. Splenectomy was performed, reduction of the herniated stomach, and repair of the diaphragm with two rows of interrupted cotton sutures. After the pleural toilet was completed the lung expanded readily with positive pressure except for the lower border of the lower lobe where there was a short laceration which was not bleeding. The chest was closed and a tube left in the 6th interspace in the posterior axillary line, another in the 2nd interspace anteriorly, both connected with water trap drainage. Débridement of the wound entrance with closure of the deep muscles over the small defect in the left pleura. The patient received 1 unit of plasma and 500 cubic centimeters of blood during the 70 minute procedure. Convalescence was smooth. Patient was sitting on the side of the bed eating a full diet on the 2nd postoperative day. X-ray films of the chest 36 hours after operation show complete expansion of lung (Fig. 1b).

CHEMOTHERAPY

Enthusiasm for chemotherapeusis in the treatment of peritonitis in civilian practice has not been borne out by our experience in war surgery. The practice of administering sulfadiazine in tablet form as soon as possible after wounding is completely contraindicated in the man with a possible abdominal wound. Peristalsis and absorption cease abruptly at the time of wounding. The tablets frequently plug the gastric tube and are often recovered from the free peritoneal cavity. In an initial group of 28 cases we adopted a regimen of intensive sulfadiazine therapy, giving 10 grams intravenously preoperatively, instilling 10 to 15 grams of sulfanilamide crystals into the peritoneal cavity, and continuing with 5 grams of sulfadiazine every 8 hours following operation. There remained cases of overwhelming contamination which were not apparently affected by this intensive therapy. We were also encountering a distressing number of renal failures and it was hard to be certain that acetylization of the sulfadiazine with the deposition of crystals in the kidney was not a factor in producing this condition.

In April, 1944, penicillin became available in sufficiently large amounts to warrant its use in cases of this type. Since that time we have used no "sulfa" drug. One hundred thousand units of penicillin were given intravenously preoperatively to every patient with likely intraperitoneal perforation of colon, 25,000 units otherwise routinely. In those patients with severe contamination or established peritonitis, 100,000 units dissolved in 200 cubic centimeters of saline have been instilled into the peritoneal cavity through a catheter directed to the major areas of contamination just prior to finishing snug closure of the peritoneum. In all patients, regardless of the presence or absence of hollow viscus perforation, 25,000 units have been routinely administered every 3 hours until the indication has no longer existed, frequently throughout the patient's 10 day stay in our units. We have observed no difference in the patients who have received penicillin except that the associated soft tissue wounds have appeared cleaner. In cases of the same type patients have continued to succumb to their contamination. Renal failure has occurred with the same frequency. We suspect that if neither drug was available the result would be the same.

It should be pointed out in this connection that these views are not thoroughly concurred in by many surgeons working with these same types of cases, particularly because of the known inefficacy of penicillin in combatting the growth of Escherichia coli and its allied organisms. There is sufficient indication that the Escherichia coli is not the lethal organism in peritonitis, but rather that the clostridii and the anaerobic streptococci are. Since both of the latter are effectively combatted by penicillin, we have felt the objection to its sole use invalid. Clinical impression would seem to substantiate this view.

POSTOPERATIVE MANAGEMENT

If a shock state exists at the completion of surgery the patient remains on the same litter on which he was operated upon, in the deep

Trendelenburg position during the continuance of resuscitation. When all blood lost seems adequately replaced plasma infusion is continued slowly (40 drops per minute). Oxygen at 8 liters a minute is given usually by means of a soft intrapharyngeal catheter. Blood pressure and pulse readings are recorded by the nursing staff at half-hourly intervals until stabilized at normal for a 2 hour period when the treatment is stopped.

Nasogastric suction is instituted through an indwelling gastric catheter, of No. 18 F. caliber when available. This suction is continued until audible peristalsis has been resumed, usually about the 4th or 5th postoperative day even when there has been extensive contamination. It was early recognized that these patients stand the administration of electrolytic solutions poorly, tending to develop pulmonary edema. The following case is illustrative:

CASE 8. An American soldier, aged 20 years, was admitted 2 hours after sustaining a penetrating wound of the left flank and abdomen by small arms fire, in profound shock, blood pressure and pulse unobtainable. Response to infusion of two units of plasma and 1500 cubic centimeters of blood was slow and the blood pressure 2 hours later was 70/40, although the pulse was 88. Operation was undertaken immediately. There was an estimated 2000 cubic centimeters of blood in the peritoneum only slightly contaminated. The missile had entered through the leaves of the mesentery of the descending colon at about its midpoint perforating it tangentially extraperitoneally, passed through the upper jejunum and entered the retroperitoneal tissues. There was a long laceration of the left common iliac vein which was bleeding briskly. The vein was doubly ligated above and below the rent. The jejunal perforation was closed and the descending colon exteriorized. Although 2000 cubic centimeters of blood was given during the procedure he was in severe shock at its close, but over the next 12 hours blood pressure and pulse were stabilized within normal range of values. There followed 2 days of very satisfactory convalescence with slight fever although the pulse remained above 120 and there was moderate oliguria, the urinary output reaching 500 cubic centimeters on the 2nd day. On the third day, an hour after the completion of the infusion of 1000 cubic centimeters of dextrose-saline and 1 unit of plasma at 40 drops a minute over a 3½ hour period, he developed sudden severe dyspnea, cyanosis, diffuse moist râles over both lung fields, and rapid, thready pulse. Because of the sudden character of the onset, the known injury to a great vein, and the absence of dilatation of peripheral and neck veins, a sublethal pulmonary embolus was suspected. After temporary improvement, 13 hours later he developed fulminating pulmonary edema, cyanosis, and died. The sole findings at autopsy were very wet, edematous lungs and a markedly dilated, flabby, edematous heart. There were no antemortem clots in any of the great veins. The peritoneum was "smooth and glistening throughout" and the jejunal perforation well closed.

This case is illustrative of the caution that must attend the administration of fluids in patients who have been in marked shock with severe cardiovascular instability.

Departure was therefore made from the usual regimen of replacing fluid loss in the presence of gastric siphonage. No fluids are given until a 24 hour interval has elapsed after the recovery from shock and fluids are then begun cautiously. A drip apparatus is introduced into the system and the administration rate kept at 40 drops a minute. One unit of plasma is added to each thousand cubic centimeters of dextrose solution to aid in maintaining plasma proteins. After twenty-four hours hematocrit, plasma protein, hemoglobin, and red blood cell determinations are made and the relative amounts of blood and plasma given are guided by the presence of hemodilution or hemoconcentration. Careful records are kept of the urinary output so as to provide a further guide in the administration of fluids.

Pulmonary complications are particularly troublesome in this type of case and every precaution must be taken to prevent the accumulation of bronchial secretions and pulmonary atelectasis. The active measures taken to this end are:

1. Careful suction toilet of the tracheobronchial tree at the close of anesthesia with bronchoscopic suction if indicated.

2. Frequent turning of the patient, manual support of the abdomen with insistence that he cough. The nursing and enlisted personnel on the wards have become particularly proficient in this maneuver.

3. Avoidance of excessive sedation depressing the cough reflex.

4. Frequent inhalation of pure carbon-dioxide inducing hyperpnea and cough.

5. Early recognition of atelectasis by frequent examination of the patient.

6. Direct removal of accumulated secretions through a catheter passed by the pharyngeal route or by bronchoscope.

The following case report illustrates many of the postoperative complications commonly encountered:

CASE 9. An American officer, aged 34 years, was admitted 7 hours after wounding by mortar fragments having received 3 units of plasma and morphine ½ grain 3 hours previously. He was in severe shock, blood pressure unobtainable, pupils pinpoint, respirations depressed. There was a large penetrating wound through the left 11th rib in the midaxillary line and multiple penetrating soft tissue wounds of both lower extremities. The pleura was intact. The signs of peritoneal irritation were present, urine negative, gastric contents normal. He was given 1 unit of plasma and 1000 cubic centimeters of blood over a period of 1½ hours, but response was slow and the blood pressure remained static at 80/40. Operation was immediately performed. There was foul blood in large amounts in the peritoneal cavity with grayish staining of the peritoneum, the loops of bowel covered with brownish-gray exudate. Five perforations of the upper 8 inches of jejunum were closed, a large rent in the splenic flexure of the colon exteriorized. The inferior third of the spleen was badly fractured, bleeding slightly, the spleen large, fibrotic with the gross appearance of chronic malaria. Splenectomy was performed. After instilling 10 grams of sulfanilamide powder into the peritoneal cavity the splenic fossa and the retrocolic spaces were drained with soft rubber drains through the flank, a third drain through the débrided and enlarged wound of entrance. With clean instruments débridement of the extremity wounds was carried out. He was given 1000 cubic centimeters of blood during and after the operation.

Postoperative regimen: Constant nasogastric suction; 2000 cubic centimeters of dextrose-saline with 15 grams sulfadiazine; ascorbic acid 200 milligrams; plasma 1000 cubic centimeters daily, in divided doses. On the second day his pulse was 140, temperature 103.8; he was restless, pulmonary edema present, the tracheobronchial tree filled with frothy, thin secretions. The trachea was aspirated by catheter at 4 to 6 hourly intervals and 100 per cent oxygen under 6 millimeters of mercury pressure begun. Intravenous fluids were stopped. On the 4th day the chest was still moist but the secretions had thickened. The colon was draining slightly, the pulse still above 120, temperature subnormal. Throughout the next 4 days both lungs remained very wet and the positive pressure oxygen was continued, 2 hours on, 1 hour off, with slow improvement. By this time the colostomy was draining copiously, the abdomen not distended. On the 9th day there was complete disruption of the wound during a coughing spell with evisceration of loops of small intestine. The wound was strapped with adhesive. He was very dyspneic, breath sounds absent posteriorly. On the following day, after removal of the nasoduodenal tube he had gross hematemesis. The tube was reinserted. On the 11th day 500 cubic centimeters of blood was given, though the red cell count was 4,280,000 and he was on continuous nasal oxygen. On the 13th day there was edema of the ankles, a part of the picture of extreme nutritional depletion. The urinary output for the first time reached 1000 cubic centimeters and occasional red cells and crystals of sulfadiazine character were seen. The veins in the neck were distended and there was gross evidence of elevated venous pressure. The liver was palpable 4 inches below the costal margins. Slow digitalization was begun. On the following day he was disoriented. All sulfonamide therapy was stopped. On the 15th day 150 cubic centimeters of clear fluid was aspirated from the left pleura and search made for subphrenic abscess. On the 16th day he was cyanotic, respirations of Cheyne-Stokes type. Distention was marked and peristalsis absent, the colostomy not functioning. At noon of that day he rapidly improved, became rational, the colostomy drained copiously and the distention ceased. The peripheral edema decreased. Aspirations of the left pleura on the subsequent 2 days obtained 250 cubic centimeters of serosanguineous fluid. On the 20th day the wound of entrance was enlarged and the left subphrenic space more adequately drained, obtaining a small amount of pus not under tension. A small abscess contiguous to the colostomy was drained. He was making general improvement and eating small amounts of food, the problem chiefly nutritional. On the 24th day a small pocket of pus near the left lower end of the wound was drained. He was evacuated to the rear on the 28th postoperative day.

He was seen again on the 55th postoperative day still running a slight febrile course, from a retrocolonic abscess following the establishment of more adequate drainage of which he improved rapidly. Letters over a year later report the closure of the colostomy stoma in the Zone of the Interior, the return to normal weight and adequate health except for the peroneal nerve palsy resulting from division of the nerve in a small wound of the left leg and the, as yet, unrepaired incisional hernia.

This patient had the most severely contaminated peritoneum from which we have seen a patient recover. His course exemplifies some of the complications that may follow which we have learned to anticipate and to avoid to a great degree.

The frequency of direct injury to large vessels of the trunk and extremity and concurrent extremity wounds often with fractures encased in plaster make venous stasis and

thrombophlebitis likely. Every possible measure must be taken to prevent this complication, especially early and frequent change of position and as early mobilization as possible. We have recognized thrombophlebitis in only 2 patients of this group, and none has developed massive pulmonary embolus.

As soon as peristalsis has begun again and the duodenal tube is removed, the patient is placed on a general diet. During the early postoperative period intravenous vitamin supplement is routinely administered, ascorbic acid in 300 milligrams daily dose, the B complex, and vitamin K. This therapy is continued by mouth as soon as it can be ingested. In spite of these measures, there is usually visibly rapid nutritional depletion of the patient who may already have suffered considerable depletion resulting from long weeks in combat.

Early experience in the African campaign demonstrated that patients who have undergone major surgical procedures or who are suffering from peritonitis do not stand transportation within the first few days of operation. Ten days has been set as the minimum ideal time for evacuation. At the end of this time many are afebrile, eating a full diet, and have begun to sit in a chair beside their cots. Under the stress of a rapidly moving front, and occasionally when evacuation of the hospital has been forced by enemy shell fire, it has been necessary to evacuate patients earlier. The average time for evacuation of this entire series was 10.7 days.

DISCUSSION

This opportunity to observe the pathology and altered physiology produced by the rapid flooding of the peritoneal cavity with the content of colon or terminal ileum has brought to our attention a pattern of events so uniform in their fatal characteristics that we prefer to speak of it as the "syndrome of overwhelming contamination." Typically, the patient is admitted in a shock state which responds slowly and incompletely to replacement therapy. When the peritoneal cavity is opened there is a large amount of foul-smelling fecal stained blood. The peritoneum is stained a purplish-brown, has a grayish cast, is lustreless, and there are areas of intense hyperemia, particularly over loops of small intestine. Fibrin deposition has not as yet begun. The patient usually goes into deep shock during the operation from which his recovery is slow, and frequently never complete. In spite of the continuance of plasma administration, he develops an intense hemoconcentration with evidences of markedly slowed circulation of the peripheral capillaries. The blood pressure gradually falls, the pulse rate rises, and death occurs in the first 24 hours. In those patients who survive for a longer period, reaching the 3rd or 4th day, there is invariably pulmonary edema. Large amounts of frothy fluid well into the trachea which they are too weak to cough up and which it is difficult to remove sufficiently well by intratracheal suction. Fever is rarely high before death occurs between the 3rd and 5th postoperative days. At autopsy one is especially impressed with the fact that the peritonitis has continued to improve. In fact, in certain cases there is the very minimal evidence of peritonitis—a few areas of peritoneum that have lost their sheen, a few flecks of fibrin. Unless there is continued leakage into the peritoneum a true fibrinopurulent peritonitis is not seen. In certain of these cases, peristalsis may have been reestablished prior to death, diet tolerated, and the colostomy may have begun to function. The major gross pathology is in lungs and heart. The lungs are intensely wet, waterlogged, the bronchi full of thin, frothy fluid. Certain areas of atelectasis and pneumonitis may be present, but the picture is chiefly one of edema rather than pneumonia. The heart is invariably very edematous, chiefly in the subepicardial layers, the myocardium pale and flabby, the entire heart dilated, especially the right ventricle.

There occur certain instances in which there is massive spillage of colon content in which there is not this peritoneal staining. Usually the feces is solid in these patients. There is usually intense hyperemia of the peritoneum and a puriform exudate with little odor. These patients live. The others die. Although it is undoubtedly important, it would seem that the picture bears little

direct relationship to the time lapse between wounding and operation (Table I).

We have no bacteriologic proof, but we suspect that the most important etiologic factor is the type of organism in the intestinal flora. Grossly, it appears that, unless there is continued leakage into the peritoneal cavity, these organisms do not continue to grow, but are satisfactorily handled by the body's defense mechanisms. The early development of a shock-like state suggests that it may be the result of bacterial exotoxins that are suffused into the blood stream with the initial spillage and subsequent dissemination of the contamination over a large absorptive peritoneal surface. The effect of these organisms on heart, lungs, and capillaries accounts for the fatal issue. This may also explain why chemotherapy does not appear to effect their course.

TABLE IX.—PRIMARY CAUSE OF DEATH—38 CASES

Shock	
Primarily hemorrhage	3
Overwhelming contamination	9
Sepsis	
Peritonitis	17
Retroperitoneal phlegmon	1
Renal failure—uremia	3
Cardiac failure (blast)	1
Postoperative hemorrhage	1
Intestinal obstruction	1
Suppurative thrombophlebitis	1
Pneumonia	1

Cases of this type must inevitably make up the large portion of the fatal cases resulting from intestinal perforation. The determination of the most likely causative organism or organisms might permit the development of an antitoxin which would be a distinct aid in tiding the patient over the critical effects of the initial contaminating dose.

TABLE X.—TIME OF DEATH

	No. deaths	Per cent
First 24 hours	10	26
Second through 7th day	22	56
After the first week	7	18

Suppression of renal function has been observed with alarming frequency by those of us who have been dealing with the most serious types of cases. Total urinary suppression has been a major cause of death in 3 cases. The following case is illustrative:

CASE 10. An American soldier was wounded by high explosive fragments 2½ hours before admission. He was in severe shock, blood pressure 40/0, pulse imperceptible. There was a penetrating wound of the left lower chest with hemothorax, multiple small wounds over the entire torso. The intraperitoneal missile had entered through the lumbar area above the iliac crest. Complete physiologic transection of the spinal cord at 11th dorsal vertebra was present at the time of admission, apparently from a small missile which had entered the right chest to the left of the 10th dorsal vertebra. Response to shock therapy was slow and incomplete after 1500 cubic centimeters of blood. On opening the peritoneum the blood pressure and pulse became at once imperceptible. There was a single small perforation of the midjejunum, the fragment lodged in the mesentery of the jejunum contiguous to the wound. There was an estimated 1000 cubic centimeters of blood free in the peritoneal cavity and brisk hemorrhage from the wound of entrance in the posterior peritoneum to the right of the base of the mesentery. There was a tear in the inferior vena cava and right common iliac vein at their junction. Ligature of the right common iliac vein and vena cava above and below their wounds. The jejunal wound was closed. The missile entering through the spine had passed through the spinous process and lamina into the left chest laying bare the epidural fat but not lacerating the dura and there was no increased intradural tension at this point. Large flank wounds were débrided. The patient was given 1500 cubic centimeters of blood during the 3½ hour procedure. He remained in shock during the next 12 hours, although alert. There was early return of function to the left leg and transient venous congestion on the right. Following 1000 cubic centimeters of plasma by slow drip and 1000 cubic centimeters of 1¼ per cent sodium bicarbonate solution during the second 12 hours the blood pressure returned to normal although the pulse remained above 132. The top temperature reading was 99.2 degrees. Urinary output by 24 hour periods was 80 cubic centimeters, 90 cubic centimeters, 75 cubic centimeters, 50 cubic centimeters, and zero. The urine contained considerable detritus and a small amount of hemoglobin. There was no evidence of hemolysis of plasma. The blood group was O and the cross-match of the samples of blood were rechecked and no agglutination found. The patient died on the 5th day after 2 days of typical uremic coma, in pulmonary edema. Necropsy showed in addition to the known pathology a small perforation of the posterior extraperitoneal wall of the ascending colon with an early fecal fistula through the large débrided wound of the back which was not badly infected. The peritoneum was smooth and glistening and the venous ligature intact. Both kidneys appeared entirely normal.

In a few cases severe oliguria has developed from which the patient has recovered. Renal suppression has been no more frequent in

abdominal cases than in other severe injuries. The one most striking feature seems to be that almost all have been for long periods in extreme hypotension states. They have therefore received large amounts of blood in the resuscitation. Only a few have shown clinical evidences of transfusion reaction and in these there has been extensive hemolysis in plasma and urine typical of transfusion reaction. Detailed studies are now being made on the problem. We feel that it has little relationship to the administration of blood, and prefer to call it "shock kidney."

Further reduction in the mortality of the abdominal wounds of warfare depends chiefly upon the solution of these two problems.

SUMMARY

1. Experience in the initial surgical care of 130 war wounds of the abdomen is presented. The mortality in our hands was 23.4 per cent.

2. Diagnosis is chiefly a problem of reconstructing the course of the missile. The usual signs of peritoneal irritation are reliable. The presence of peristalsis rules out intraperitoneal perforation of hollow viscus.

3. It is profitable to operate on every patient with an abdominal wound regardless of time lapse or risk.

4. Exploratory celiotomy is rarely necessary.

5. The degree of shock on admission is the most reliable prognostic sign.

6. Severe fecal contamination of the peritoneum produces a clinical picture impossible to differentiate from shock. These patients respond slowly or not at all to replacement therapy.

7. Shock treatment is continued as long as improvement continues. It is rarely profitable to give more than 1500 cubic centimeters of blood prior to operation.

8. Ether-oxygen anesthesia by closed absorption endotracheal technique is the anesthetic of choice.

9. Although the function of the surgeon is primarily to save life it is rarely necessary to adopt compromise procedures.

10. Resection of small bowel is preferable to multiple closures within a short segment which may distort and lead to obstruction.

11. Exteriorization of the wounded colon is the safest procedure. Perforation of the colon remains the single most lethal factor in any series of abdominal wounds.

12. Adequate drainage of liver wounds is essential. Liver packs are rarely, if ever, necessary and are productive of complications.

13. Solid viscera, including the spleen, do not continue to bleed significantly from their parenchyma.

14. Intractable bleeding from a hilar vessel and division of the ureter form the sole indications for removing the wounded kidney.

15. Closure of the diaphragm is as important on the right as on the left.

16. Penicillin is no more effective than the sulfanilamides in preventing death from severe contamination of the peritoneum.

17. Intravenous administration of isotonic electrolytic solutions postoperatively is poorly tolerated by the patient recovering from a severe shock state or combatting peritonitis.

18. Pulmonary complications must be anticipated and vigorously treated.

19. Overwhelming contamination of the peritoneum and renal insufficiency remain the two problems the solution of which must precede marked further reduction of mortality from abdominal wounds.

REFERENCES

1. BURBANK, BENJAMIN. Personal communication, 1944.
2. COLCOCK, BENTLEY P. Bull. U.S. Army M. Dept., 1944, 80: 106-109.
3. MICHELS, LEON M. Preoperative diagnosis of the recently wounded abdomen. To be published.

THE EFFECTS OF PEDICLE JEJUNAL TRANSPLANTS IN THE STOMACH ON MANN-WILLIAMSON DOGS

HARRY C. SALTZSTEIN, M.D., F.A.C.S., and IRVIN J. KURTZ, M.D., Detroit, Michigan

ANDRUS, Lord, and Stefko reported that when pedicle grafts of the jejunum were transplanted into the stomach wall of dogs a reduction in gastric acidity ensued. In such animals, following histamine injections there was a reversal or considerable diminution in the expected rise in acidity. These results were obtained particularly with jejunal transplants, although a duodenal flap caused similar changes but in a lesser degree. No effects were produced with ileal or colonic segments.

They then produced gastroduodenal ulcerations by the injections of histamine-beeswax mixture after the method of Varco. Jejunal transplants into the stomach had a salutary effect on these ulcers. In 3 dogs previously prepared with grafts, no ulcers formed after histamine-beeswax injections.

Applied to humans (2) jejunal flap transplants were done in 4 peptic ulcer cases. Hyperacidity was reduced in 3 of these patients and clinical improvement without change in acidity was noted in the fourth patient.

In ulcers produced by the histamine-beeswax method, the beeswax is imbedded in the subcutaneous tissues. The secretogogue effect of the histamine causes continuous gastric hypersecretion. Chronic ulcers form in the stomach or duodenum in 100 per cent of cases.

Another standard method of producing chronic duodenal ulcers in dogs is the Mann-Williamson operation (6). In this procedure the stomach is made to empty into the jejunum, and the alkaline duodenal bile and pancreatic juices are diverted into the terminal ileum. Acid gastric juice thus spurts constantly against an area of jejunum, unprotected by its normal alkaline juices.

From the Experimental Surgical Laboratory, Harper Hospital, Detroit, Michigan. Aided by a grant from the Mendelson Fund.
Prepared for presentation before meeting of Central Surgical Society in February, 1945, canceled.

We have done the Mann-Williamson operation on 28 control dogs whose diet consisted of left overs from the hospital kitchen. In all cases (100%) jejunal ulcers were demonstrated at necropsy. The survival time averaged 71 days. The minimal time from operation to expiration was 13 days, and the maximum, 135 days (7).

We wish to report our observations on 6 Mann-Williamson dogs in which jejunal pedicle graft transplants were done (Table I). These operations were done in one or two stages.

TECHNIQUE

Intravenous nembutal anesthesia was used. The abdomen was opened through a midline incision. A segment of jejunum 1½ to 2 inches long and 3 to 4 inches from the ligament of Treitz was isolated and divided. Meticulous attention was given to the integrity and adequacy of the attached mesenteric blood supply.

The posterior wall of the stomach was then delivered through a rent in an avascular portion of the mesocolon and serosal sutures were placed joining the prepared section of jejunum to the stomach. The cylinder of jejunum was then incised at its antimesenteric border and the edges were trimmed, thus forming a flap. A gastric window was fashioned to accommodate the jejunal patch, and the pedicle graft was secured in place with two rows of sutures, usually silk throughout.

When the jejunal transplant was done as a first stage or preliminary procedure, the continuity of the jejunum was then re-established either with a side-to-side, or end-to-end anastomosis, and the abdomen was closed.

The second stage consisted of the typical Mann-Williamson operation. The stomach was divided at the pylorus, and the duodenal end was inverted and closed. The jejunum was sectioned about 1 inch distal to the previous anastomotic site. The open pyloric end of the

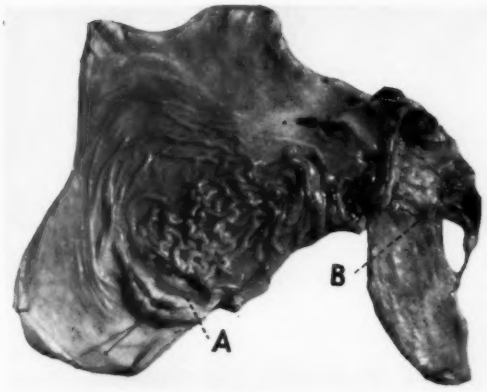


Fig. 1a.

Fig. 1b.

Fig. 1c.

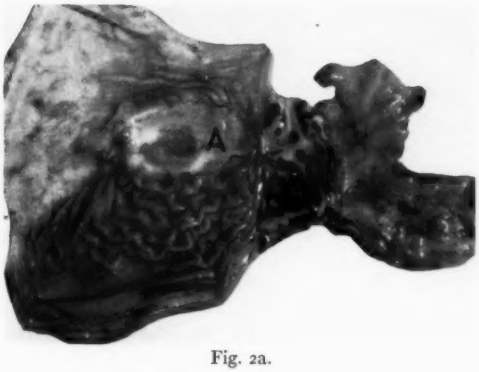


Fig. 2a.

Fig. 2b.

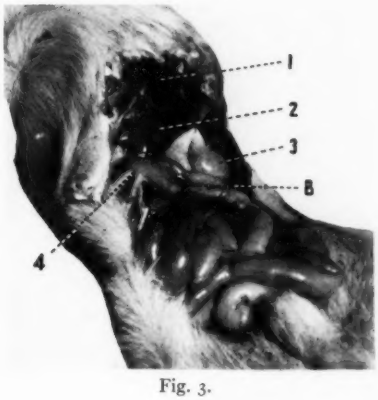


Fig. 3.

Fig. 1. Dog No. 225. One stage jejunal pedicle graft and Mann-Williamson operation; death in 32 days. a, Pedicle graft viable, *A;* jejunal ulcer, *B*. b, Closeup of ulcer. c, Microscopic appearance of jejunal ulcer.

Fig. 2. Dog No. 208. One stage jejunal pedicle graft and Mann-Williamson operation; death in 64 days. a, No jejunal ulcer, *A;* well defined penetrating ulcer jejunal transplant. b, Microscopic section through ulcer in center of transplant. Note necrotic superficial layer of ulcer and normal appearance of blood vessels in base of transplant.

Fig. 3. Dog No. 224. One stage operation; death in 86 days; perforated jejunal ulcer with evidence of fresh intraperitoneal hemorrhage. Autopsy appearance: perforated jejunal ulcer with fresh hemorrhage, *B*; under surface of diaphragm (torn), *1*; liver, *2*; stomach (pyloric end anastomosed into jejunum), *3*; closed stump of duodenum, *4*.

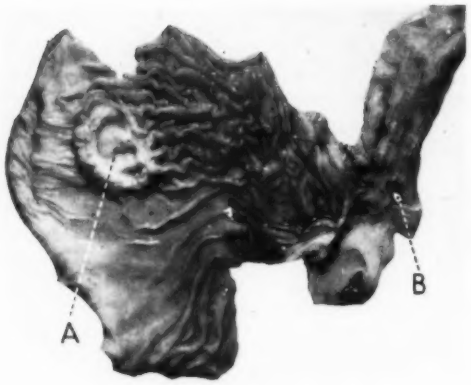
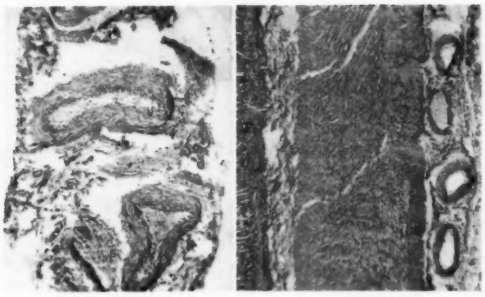


Fig. 4a.



b c

Fig. 4. Dog No. 224. Same dog as in Figure 3. a, Pedicle flap, *A*; perforated jejunal ulcer, *B*; note marked jejunitis. b, Cross section of vascular pedicle of jejunal flap; note normal appearance of blood vessels. c, Section of wall of pedicle flap in stomach; note blood supply and normal appearance of all layers.

stomach was anastomosed into the distal jejunal segment. The proximal jejunum was then joined to the terminal ileum (8 to 10 inches from the ileocecal junction) thereby providing the surgical duodenal drainage. Anastomoses were generally side-to-side or end-to-side, occasionally end-to-end. Silk was used throughout. The two stage operation was done in 3 dogs. The interval between the 2 operations was 25, 29, and 47 days, respectively.

Because of the technical difficulties of adhesions encountered when the abdomen was entered a second time, the two procedures were combined in one operation in 4 animals. When thus performed, the pedicle graft was fashioned into the posterior stomach wall first. Then the stomach was divided at the pylorus and the duodenum was closed. The open ends of the jejunum where the transplant has been removed were then used for the Mann-Williamson anastomoses: the distal one for the pyloric end of the stomach, the proximal one joined to the terminal ileum.

TABLE I.—RESULTS

Dog	Surgery	Survival time—days	Autopsy findings	Laboratory data				
				Wt. loss %	Hgb. %	R.B.C.	W.B.C.	Days before exitus
225 (Fig. 1)	One stage jejunal pedicle graft and Mann-Williamson 12-20-44	36	Superficial jejunal ulcer pedicle graft viable	30	25	1,950	11,600	4
208 (Fig. 2)	One stage operation 11-7-44	64	No jejunal ulcer. Well defined ulcer of pedicle transplant. Pedicle blood supply O.K.	40	40	3,650	13,000	3
224 (Fig. 3) (Fig. 4)	One stage operation 12-17-44	86	Perforated jejunal ulcer fresh intraperitoneal hemorrhage. Pedicle transplant O.K.	50	49	3,150	8,950	15
204 (Fig. 5)	Two stage operation Pedicle graft jejunum into stomach 11-1-44	56	Two superficial jejunal ulcers. Pedicle graft O.K.	25	32	2,400	19,400	4
	Mann-Williamson 11-30-44	28						
205 (Fig. 6)	Two stage operation Pedicle graft 11-3-44	157	Deep jejunal ulcer 1½ cm. diameter. Pedicle graft O.K.	53	40	3,350	10,650	8
	Mann-Williamson 11-28-44	132						
182 (Fig. 7)	Two stage operation Pedicle graft 3-13-44	126	Two deep jejunal ulcers, one with perforation. Pedicle graft O.K.					
	Mann-Williamson 4-29-44	79						

Fig. 5a.

Fig. 5b.

Fig. 6.

Fig. 7.

Fig. 5. Dog No. 204. Two stage operation; first stage jejunal transplant, second stage Mann-Williamson operation 25 days later; death 28 days after operation. a, Jejunal transplant, *A*; two large eroding jejunal ulcers, *B*, *C*. b, Microscopic section through ulcer *B*.

Fig. 6. Dog No. 205. Two stage operation; jejunal transplant; Mann-Williamson operation 15 days later; death 42 days after operation. Jejunal transplant, *A*; jejunal ulcer 1½ centimeters in diameter, *B*.

Fig. 7. Dog No. 182. Two stage operation; jejunal transplant and Mann-Williamson operation 18 days later; death 51 days after operation. Jejunal pedicle graft, *A*; two deep jejunal ulcers, *B*, *C*, one of which, *B*, has perforated.

RESULTS

In Table I it will be noted that despite pedicle jejunal graft transplants, all dogs except one developed jejunal ulcers. The one exception, dog No. 208, developed an ulcer of the jejunal pedicle transplant (Fig. 2). The ulcers were identical with the ones we have been accustomed to seeing with control Mann-Williamson dogs. The photographs show this clearly. There are superficial ulcers, ulcers penetrating into the muscularis, and ulcers which have perforated completely. They form in the identical location—½ centimeter beyond the pylorojejunal anastomosis or slightly distal to this point as they did in our controls. Two of the photographs show that the blood supply at the base of the transplant (and also in the vascular pedicle) is intact.

The survival time average, 70 days, was about the same, 71 days, as in our control animals.[1]

CONCLUSION

The healing and prophylactic effects attributed to the jejunal flap in dogs with histamine induced ulcers, were not evident in 6 dogs with

[1] The seventh experiment was not completed at the time this paper was submitted. It was a one stage operation done on December 20, 1944. The dog was sacrificed August 17, 1945, (8 months later) at which time there was 37 per cent weight loss and the dog was almost moribund. Autopsy showed a large well nourished pedicle graft. The jejunum showed no ulceration (Fig. 8). Since this was one of the larger jejunal grafts, further work will be done using even larger transplants.

the Mann-Williamson ulcers. Ulcers formed, eroded and perforated in spite of viable grafts. The seventh dog was sacrificed 8 months after operation. There was no ulcer present in this animal.

NOTE: Since this work has been completed, two articles have appeared testing the value of pedicled jejunal transplants on gastric acidity: Kolouch, Dubus and Wangensteen reported that the histamine effect was not reversed in pedicle transplant dogs, as Andrus and associates had found. Also, when daily intramuscular injections of histamine in beeswax were given, the jejunal transplant showed reduced resistance, and invariably ulcerated in the presence of this induced continuous gastric hypersecretion. Using Heidenhain's pouch dogs, the pedicle graft caused a slight but inconstant depression of gastric acidity, but it did not regularly inhibit gastric secretion from the pouch and gastric juice from such a pouch was as irritating as normal gastric juice when dripped onto exteriorized duodenal mucosa.

Grossman, Dutton, and Ivy also tested the gastric acid secretory response to histamine stimulation in pedicle jejunal grafts. They found no significant change.

REFERENCES

1. ANDRUS, W. DE W., LORD, J. W., and STEFKO, P. Proc. Soc. Exp. Biol., 1943, 52: 99.
2. Idem. Ann. Surg., 1943, 118: 499.
3. IVY, A. C., GROSSMAN, M. I., and DUTTON, D. F. Surgery, 1945, 17: 685.
4. KOLOUCH, FRED, JR., DUBUS, ALFONSO, T. S., and WANGENSTEEN, O. H. Surgery, 1945, 17: 667.
5. LORD, J. W., JR., ANDRUS, W. DE W., and STEFKO, P. Proc. Soc. Exp. Biol., 1943, 52: 100.
6. MANN, F. C., and WILLIAMSON, C. S. Ann. Surg., 1923, 77: 409.
7. SANDWEISS, D. J., SUGARMAN, M. H., FRIEDMAN, M. H. F., SALTZSTEIN, H. C., and FARBMAN, A. A. Am. J. Digest. Dis., 1941, 8: 371.
8. STEFKO, P., ANDRUS, W. DE W., and LORD, J. W., JR. Science, 1942, 96: 208.
9. VARCO, R. L., CODE, C. F., WALPOLE, S. H., and WANGENSTEEN, O. H. Am. J. Physiol., 1941, 133: 475.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBES

KARL A. LOFGREN, M.D., and MALCOLM B. DOCKERTY, M.D., Rochester, Minnesota

PRIMARY carcinoma of the fallopian tubes is a rare disease. Its infrequent occurrence is especially evident when it is compared with the rather frequent incidence of malignant neoplasia in the uterus and the ovaries, which, with the tubes, originate from the muellerian duct. Moreover the clinical manifestations of tubal carcinoma are so protean that the internist rarely arrives at a correct diagnosis even when the process is far advanced. At the operating table the surgeon often is confused by the appearance of hydrosalpinx and may fail to realize that a distended condition of the fallopian tubes may obtain on a malignant basis. He consequently may be led to carry out an inadequate sacrifice of tissues. Even the pathologist has difficulty in differentiating from carcinoma of the tubes such divergent lesions as adenomyosis and tuberculous salpingitis. In consideration of the aforementioned facts and the added knowledge that primary tubal carcinoma carries an extremely bad prognosis, attempts made along the line of establishing criteria for early diagnosis of the condition would seem to fulfil a worthy purpose. Our contribution consists of a review of the literature and the clinical and pathologic analysis of 16 cases of primary carcinoma of the fallopian tubes seen and studied at the Mayo Clinic in the past 40 years.

HISTORICAL DATA

Orthmann in 1888 described what is now generally accepted as the first authentic case of primary carcinoma of the fallopian tube. Although he collected, reviewed, and accepted 13 earlier examples from the literature, examination of these cases in the light of more recent knowledge leads to the belief that they were instances of metastatic rather than of primary involvement. Doran(6) in 1888 recorded the second well established example and expressed the opinion that the growth had its origin in a benign tubal polyp. Kaltenbach in 1889 reported the third case and described the papillary and alveolar pictures which are now almost standard in descriptions of the microscopic appearance of the lesions. Routier in 1893 and Tuffier in 1894 furnished the fourth and fifth cases respectively according to Holland. In 1901 Le Count was able to review 21 cases from the literature and to point out the frequent association of hyperplastic salpingitis as a possible etiologic factor. In 1911 von Franqué emphasized the frequent occurrence of tuberculous salpingitis as a precursor of tubal carcinoma and this was again stressed by L'Esperance in 1917 in a review of 49 cases of primary carcinoma of the fallopian tube accumulated from the literature. L'Esperance described a case of epidermoid carcinoma of tubal origin, a type of lesion first recorded for this location in 1916 by Barrett. The number of authentic examples of primary tubal carcinoma had reached the hundred mark in 1910 when Doran(7) supplemented his original report. Along with Orthmann and Vest this investigator pointed out the difficulties of diagnosis, the tendency toward early dissemination and the gloomy prognosis; Vest stated that surgical operation offered a little less than a 4 per cent chance of cure. With stimulated interest in the subject, reports of individual cases of this rare disease found their way into the literature so that Kahn and Norris in 1934 were able to collect published data on 323 cases. This number was increased to 427 when Mullins and Mosteller reviewed the subject in 1942. With the cases published in the past 2 years added to those of the present series the accumulation has now reached 450.

MATERIAL AND METHODS

The investigation of the material for the present study began with a search of the files of the Mayo Clinic for cases in which car-

From the Mayo Foundation, and the Division of Surgical Pathology, Mayo Clinic.

Abridgment of thesis submitted by Dr. Lofgren to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Surgery.

Since this paper was written Dr. Lofgren has entered the armed services and is now Lieutenant in the Medical Corps of the United States Navy.

cinoma involved principally the fallopian tube or tubes. Forty-two such cases had been encountered over a 34 year period from 1910 to 1943 inclusive. The pathologic specimens, removed surgically or at necropsy, were all available and were inspected grossly to exclude those cases in which the tubal involvement was obviously metastatic in nature. Excluded also were those cases in which massive involvement of the pelvic viscera made it unlikely that the matter of primary tubal origin of the malignant growth could be decided with certainty. Selected for further investigation were specimens in which the involvement was strictly limited to the tubes and a second "doubtful" group in which although concomitant involvement of the uterus and ovaries was present, it appeared to be grossly of a metastatic nature. No cases in which the tubal mucosa remained intact were accepted for study. In every instance multiple blocks of tissue were removed from involved and uninvolved portions of the tube and from the associated ovarian and uterine lesions when the latter were present. These blocks were placed in a fresh 10 per cent solution of formaldehyde (3.7 per cent commercial formalin), sectioned at 7 microns with a freezing microtome and stained routinely with hematoxylin and eosin. In cases in which mucus seemed to be present in sections stained by the aforementioned method, sections cut from paraffin blocks were stained with mucicarmine. The microscopic finding of psammoma bodies and of papillary mucous carcinoma, when tubal and ovarian lesions coexisted, was considered as being fair evidence that the primary lesion was in the ovary. Similarly the finding of adenoacanthomatous zones in a lesion involving the uterus and the tube or tubes was conceded as indicating a uterine origin. Discarded along with these samples after careful microscopic study were 2 specimens of tubal tuberculosis with epithelial hyperplasia. A residue of 16 cases of true primary tubal carcinoma remained to serve as a basis for this report.

CLINICAL AND PATHOLOGIC DATA

Incidence. Sixteen primary carcinomas of the fallopian tube were found in approximately 10,000 patients suffering from primary malignant lesions of the female generative tract, an incidence of 0.16 per cent. Stuebler and Brandess in a comparable analysis found an incidence of 0.45 per cent. Anspach found only 1 instance of primary tubal carcinoma among 19,439 patients admitted to the gynecologic service at the University Hospital in Philadelphia.

Age. The average age of our 16 patients was 50.9 years with extremes of 34 and 65 years. Nine of the 16 patients had passed the menopause. In the literature, 18 and 80 years represent the extremes of age for patients suffering from the effects of primary carcinoma of the fallopian tube. According to Wechsler 66 per cent of the patients affected are between the ages of 45 and 55 years, almost a decade prior to the peak incidence seen in cases of uterine (fundal) carcinomas.

Symptoms. The commonest complaint was vaginal discharge. This was present in 10 of the 16 cases and in 7 it was the principal symptom. Duration had varied from 3 days to 1 year with an average of about 5 months. In postmenopausal patients the discharge was constant and in younger women it was described as being intermenstrual. The character of the discharge varied from leucorrhea to frank bleeding. In only 1 instance was it described as malodorous. In 1 case the discharge had continued without interruption following curettage of atrophic endometrium. Throughout the literature this phenomenon, namely, persistence of discharge following curettage, has been repeatedly emphasized as being characteristic of the vaginal discharge associated with tubal carcinoma as opposed to other lesions causing this symptom (22, 30). According to Anspach other characteristics of this symptom include the occurrence of the discharge in sudden "gushes" accompanied by paroxysms of cramp-like pain, a phenomenon to which the term "hydrops tubae profluens" has been applied.

Pain in the lower portion of the abdomen usually on the side of tubal involvement was the second commonest symptom and it was a major complaint in 8 of the 16 cases. In 1 case constant, dull pain had been present for 15 years; it probably was related to the

chronic pelvic inflammatory condition associated with the tubal carcinoma. In the other 7 cases the pain was usually of shorter duration than the vaginal discharge. The pain was crampy and intermittent in character in 6 of these 7 cases and seemed to be related pathologically to distention of the affected tube produced by the expansion of the malignant growth. In 1 case, however, the pain took the form of an acquired dysmenorrhea and it was accordingly impossible to correlate etiologically with the pathologic lesion in the fallopian tubes. Pain was a prominent symptom in 53 per cent of the cases of tubal carcinoma analyzed by Doran. Fullerton felt that it was produced by stretching of the muscular coats of the tubal wall.

Three patients complained of lower abdominal swelling which had been present for from 3 weeks to 2 years. In 1 of these cases the swelling appeared to obtain on the basis of the size of the carcinoma per se whereas in the other 2 the presence of associated hematosalpinx augmented the bulk of the tubal neoplasm. In the literature this symptom is listed along with vaginal discharge and pelvic pain as completing a triad frequently based on the presence of primary tubal carcinoma.

Symptoms of a miscellaneous nature, commonly found among women suffering from various gynecologic lesions, included backache, a bearing-down feeling, constipation, dysuria, frequency, menometrorrhagia, and so forth. In our series they did not occur in any combination or in any sequence which could be interpreted as being diagnostic of the underlying tubal disorder.

Physical findings. In 14 of the 16 cases masses were demonstrated on pelvic examination. These were described as varying from 4 to 15 centimeters in average diameter and were generally nontender. The right side was given as the location in 5 instances, the left in 1 and in 1 bilateral masses were palpated. An anterior and a posterior relation to the uterus were described in 2 cases each and in the remainder the lesion was either too large or too ill defined for more accurate localization than that denoted by the term "pelvic." In about half of the cases the masses seemed movable whereas fixation of varying degrees characterized the rest of the tumors. One of the patients was suffering from the effects of an abdominal sinus tract which had developed after an operation elsewhere for pelvic inflammatory disease. Carcinomatous tissue curetted from this sinus tract suggested the diagnosis of primary tubal carcinoma but in none of the other cases was the true nature of the lesion suspected clinically as one would expect from lack of specificity of symptoms and results of examination. In the literature although primary tubal carcinoma is productive of palpable pelvic masses, the diagnosis is established preoperatively only through the medium of unusual circumstances such as that just cited. Falk in 1898 established it in 1 case by examination of material aspirated through the cul-de-sac by means of a needle and syringe. Martzloff in 1940 duplicated the feat by finding atrophic endometrium in a woman who complained of a watery vaginal discharge and who had a right adnexal mass which was demonstrated on pelvic examination.

Surgical findings. The gross appearance of primary tubal carcinoma as seen at the time of surgical exploration was often deceptive. In 6 instances the involved tubes were distended, particularly at their fimbriated extremities; the condition resembled hydrosalpinx, pyosalpinx, or hematosalpinx. In these 6 cases no adhesions and no carcinomatous implants were present and the true nature of the lesion was not suspected until the tubes were opened in the laboratory. In 4 cases unilateral or bilateral tumor masses had produced adhesions to neighboring structures, such as the uterus, the sigmoid, the cecum, or loops of small intestine. In this group there was a marked resemblance to chronic tuboovarian inflammatory disease. In the remaining 6 cases the correct diagnosis was anticipated by the finding of adhesions near the growth plus malignant appearing implants on the surface of the corresponding or the contralateral ovary, the posterior surface of the uterus, the sigmoid, or the cecum. In 2 cases the corresponding broad ligament was infiltrated by carcinomatous tissue. One of the patients had associated ascites which appeared to obtain on a malignant basis. The operative

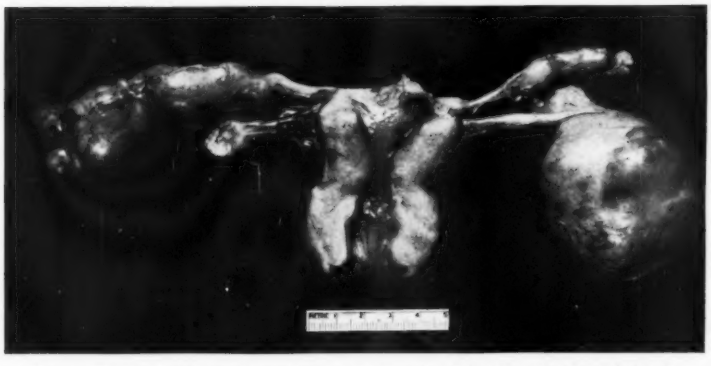


Fig. 1. Encapsulated small carcinoma primary in right tube. The fimbriated extremity of the tube has become occluded and the general similarity to pyosalpinx is apparent. The right ovary is atrophic and the left contains a dermoid cyst.

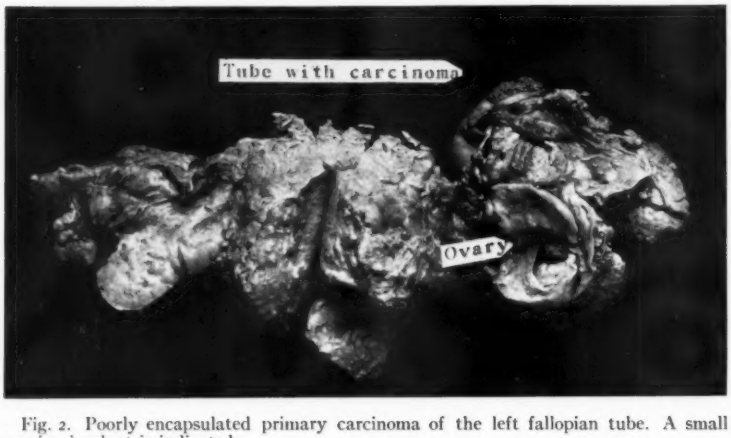


Fig. 2. Poorly encapsulated primary carcinoma of the left fallopian tube. A small ovarian implant is indicated.

procedure in these 16 cases was hysterectomy with bilateral salpingo-oophorectomy because of the laboratory diagnosis of tubal carcinoma from fresh tissue. In 2 cases dissection of pelvic lymph nodes also was performed. In 2 cases an attempt was made to remove local peritoneal implants but in only 10 cases was the surgeon at all satisfied that he had eradicated the gross evidences of malignant disease.

Pathologic data. Gross appearance. The right fallopian tube was involved in 8 and the left in 7 cases. The incidence of bilateral involvement was 6 per cent, about a quarter that reported in the literature. The size of the lesions varied from 20 by 15 by 10 centimeters to 2 centimeters in average diameter. The size of several of the larger lesions seemed to be augmented by the presence of associated hydrosalpinx or hematosalpinx. As indicated in the foregoing, 6 of the lesions were encapsulated whereas the remainder were adherent and frequently demonstrated carcinomatous extension in the form of superficial nodules or distant implants. For the most part the growths seemed to involve the outer or more distensible portions of the tube (Figs. 1 and 2). From 1 of the carcinomas a sinus tract lined by malignant tissue had extended from the right fallopian tube to the anterior abdominal wall. Hematosalpinx was found in 3, hydro-

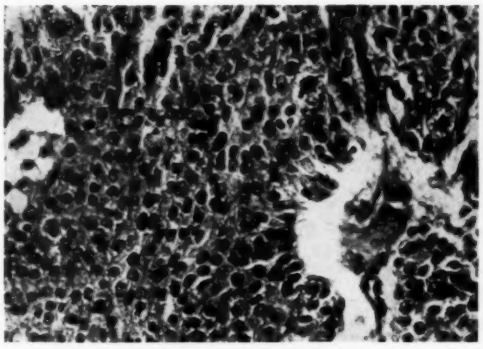


Fig. 3. Primary squamous cell epithelioma, grade 3, of the left fallopian tube. The pathologic mitosis (upper left), the absence of pearly bodies, and the general variability in the size of the cells and of the nuclear staining are indicative of rapid growth. Hematoxylin and eosin stain. ×251.

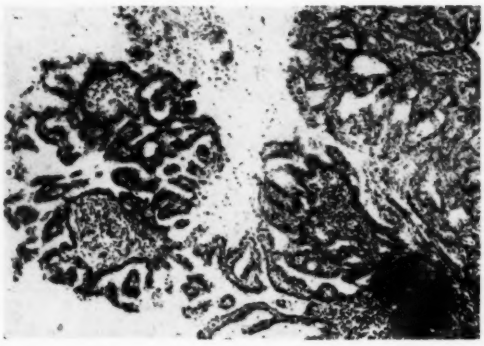


Fig. 4. Primary papillary adenocarcinoma, grade 1, of the right fallopian tube. Papillary projections are delicate and covered by one or two layers of hyperchromatic tumor cells which however appear to be fairly well differentiated. The psammoma body (dark) is a rather unusual finding. Hematoxylin and eosin stain. ×63.

salpinx in 2, and pyosalpinx in 2 of the involved tubes. In the remainder the tubal distention obtained on the basis of proliferating carcinomatous tissue per se. Grossly this tissue appeared to be papillary in 8 of the tumors whereas in the remainder no particular gross architecture was manifest, the tissue being grayish red, soft, friable, and frequently necrotic. In 6 tumors a superficial attachment to the capsule was noted but in the remainder there was evidence of invasion with peritoneal involvement in 8. Uninvolved portions of the tubes appeared grossly to be thickened and inflamed; subacute and chronic salpingitis affected the contralateral fallopian tube in 10 of the cases exclusive of the one in which the malignant lesion was bilateral. Watkins and Wilson remarked on the close resemblance between tubal carcinomatous and inflammatory lesions. In both the ostium of the tube tends to become occluded or attached to the homolateral ovary with the formation of a tuboinflammatory mass. In this way spillage of carcinoma cells may be averted until the growths are large (23).

Associated ovarian pathologic lesions consisted of malignant implants in 2 cases, dermoid cyst in 1 case, simple cysts in 2 cases and perioophoritis usually of the homolateral ovary in 6. The uteri harbored peritoneal implants in 3 cases and in 5 were the seat of multiple fibromyomas. In this series no metastasis to the endometrium was encountered as reported by Thaler, Bower and Clark, Ries, Mueller, and von Franqué.

Microscopic features. The microscopic features found in our cases of primary tubal carcinoma differed in no major respects from those described in standard treatises on the subject (6, 7, 12, 15, 16) and will be described only briefly. The essential composition was that of epithelial cells which were short, columnar to cuboid and devoid of cilia. Nuclei were large and hyperchromatic with prominent nucleoli and mitotic figures whose frequency in general paralleled the degree of dedifferentiation of the tumor cells. According to the classification and method of grading devised by Broders one of the tumors was epidermoid carcinoma, grade 3 (Fig. 3) whereas the remaining 16 tumors (1 bilateral) were classified as adenocarcinomas. The degrees of dedifferentiation in this adenocarcinoma group were such that in 1 tumor it was graded 1, in 10 graded 2, and in 3 graded 3. The remaining 2 tumors were of a grade 4 order of malignancy. The lesions of grade 1 and grade 2 malignancy were practically all papillary with single or double layers of fairly well differentiated tumor cells investing the surfaces of delicate connective tissue cores which provided coarse finger-like or delicate filamentous supporting trellises (Fig. 4). These lower grade neoplasms did not appear to be as

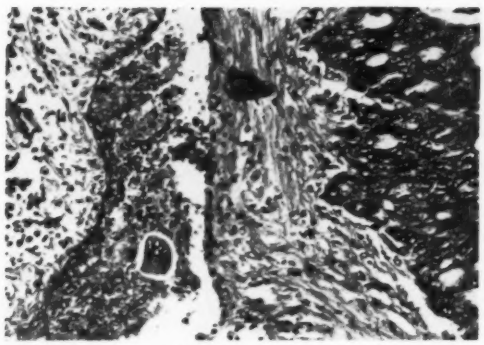


Fig. 5. Alveolar adenocarcinoma, grade 3, of the fallopian tube showing cellular anaplasia, poor alveolar formation and invasion of the muscularis. A foreign body giant cell is present in a large vein. Hematoxylin and eosin. ×148.

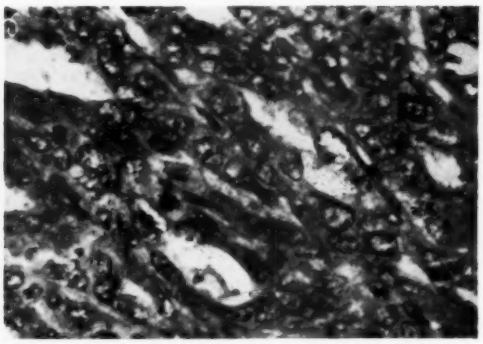


Fig. 6. Adenocarcinoma, grade 4, of the right fallopian tube. Cellular atypia, nuclear hyperchromatism, many mitotic figures indicate anaplasia. A poorly formed acinar space just above and to right of center is all that indicates glandular tissue origin. Hematoxylin and eosin. ×351.

infiltrating as the others. In the lesions of grade 3 and 4 malignancy the picture corresponded to the alveolar pattern described in the literature (Fig. 5). Here papillary formations were for the most part absent and only poor glandular formation was apparent. Mitotic figures were numerous and frequently atypical forms were seen. Giant tumor cells, perivascular growth, the occurrence of zones of necrosis and the plugging of lymphatic spaces (2 cases) and blood vessels (1 case) bespoke marked degrees of malignancy (Fig. 6). In 8 of the cases the entire growth appeared to be localized within the confines of the stretched-out tubal peritoneum whereas in the remainder there was evidence of extension with frequent involvement of what the surgeon described as surface adhesions.

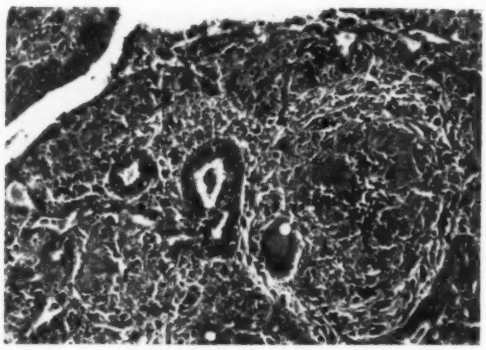


Fig. 7. Tubal tuberculosis illustrating the concomitant epithelial hyperplasia which sometimes misguides the pathologist into making the additional diagnosis of carcinoma. Hematoxylin and eosin. ×118.

In common with other investigators we found an almost 100 per cent incidence of subacute or chronic inflammatory changes in the so-called normal portions of tubes that were the seat of carcinoma. However, we were unable as a result of our studies to decide whether the carcinoma developed secondarily or whether the inflammatory process represented a reaction to the necrosis resulting from the breakdown of malignant tissue. The former possibility has been proposed and it is supported by (1) the occurrence of carcinoma in the ampullary portion of the tube which is the seat of election for the development of tubal inflammation and (2) the finding of hydrosalpinx, pyosalpinx, and hematosalpinx in the contralateral tube as noted in 9 of our cases.

The concomitant occurrence of tubal tuberculosis and tubal carcinoma has been emphasized in the literature (8, 10) and an etiologic relation has been postulated. However it is well known that tuberculous salpingitis is frequently productive of marked epithelial hyperplasia often with the formation of papillary and alveolar configurations. The appearance may suggest carcinoma and indeed in 2 of our earlier cases the condition had been so labeled. These 2 cases were eliminated from our series because, although the archi-

tecture when seen under low-power magnification suggested a malignant process associated with tuberculosis, examination under high magnification failed to reveal cellular atypia, mitotic figures, lymphatic invasion and the other criteria of malignancy which were so prominent in other cases (Fig. 7). In 1 of our cases tuberculous salpingitis involved the contralateral fallopian tube.

None of the tumors seemed to arise in connection with tubal endometriosis. Tubal adenomyoma was demonstrated in 1 of our specimens but at some distance from the carcinoma. Wrork and Broders (5, 31) have shown that tubal adenomyomas involve principally the uterine or isthmic portions of the tube and that the lesions are nearly always bilateral. The location and distribution of these lesions are accordingly unlike that of primary carcinoma of the tube. No etiologic relation between tubal polyps and tubal carcinoma was evident from the examination of our material.

End-results of treatment. Two of 16 patients are living 10 and 14 years after operation. In both of these cases the lesions were small and there was no extension beyond the presence of an ovarian nodule in 1 case in which the ovary was attached to the fimbriated end of the tube. Nine of the patients are known to be dead. The average postoperative survival in this group was 18 months with extremes of 4 months and 5 years. All grades of malignancy were represented in this group with the duration of survival being generally longer when the grade of the tumor was low rather than high. Postoperative roentgen therapy appeared to delay the fatal outcome in 1 of these 9 patients. Four of the patients have been operated on too recently to permit conclusions as to prognosis but the presence in 2 of peritoneal implants does not suggest a happy prospect. The 16th patient has not been heard from. It is accordingly apparent in our series that primary tubal carcinoma carries a gloomy outlook from the standpoint of successful treatment. A high grade of malignancy, the presence of peritoneal metastasis and the finding of malignant invasion of lymphatic spaces and of blood vessels appeared to be unfavorable features.

SUMMARY AND CONCLUSIONS

Primary carcinoma of the fallopian tube is a rare condition which accounts, in our experience, for only 1 out of every 625 carcinomas of the female genital tract. For the most part it is a disease of the menopause and has not been reported among individuals in their prepuberal years. Symptoms are insidious in their onset with vaginal discharge, pelvic pain, and abdominal tumor representing cardinal symptoms which, however, rarely lead the physician to a correct preoperative diagnosis. The evolution of the disease is more rapid than is indicated by its symptomatology, and the majority of patients so afflicted demonstrate lesions of doubtful resectability at the time of surgical exploration. The appearance of the lesion on gross inspection is sometimes deceiving since it may mimic closely familiar tubal conditions of an inflammatory nature. Because of this every distended fallopian tube should be opened before it is removed from the operating room. Treatment of these carcinomas, whenever found, regardless of any apparent state of encapsulation, should consist of total abdominal hysterectomy with bilateral salpingo-oophorectomy in addition to removal of any discernibly involved regional lymphatic nodes and peritoneal implants. Postoperatively roentgen therapy should be administered. In spite of these measures the number of 5 year cures is disappointingly small. Pathologists who are unfamiliar with the condition will often have difficulty establishing the primary nature of the lesion and should remember that the fallopian tubes are frequently involved in metastasis from ovarian and uterine sources. Actual involvement of the tubal mucosa, strict confinement to the fallopian tube, a marked disproportion between the size of the tubal and extratubal lesions as well as a working knowledge of the histologic pictures of primary uterine, tubal and ovarian carcinomas will be helpful in deciding the primary source in doubtful cases. The epithelial hyperplasia associated with tuberculous salpingitis should be kept in mind and the diagnosis of tubal tuberculosis and carcinoma should not be made except when malignant neoplasia is manifestly indicated.

REFERENCES

1. Anspach, B. M. Am. J. Obst., 1930, 20: 571-581.
2. Barrett, Lady. Proc. R. Soc. M. (Obst. Gyn. Sec.), 1916, 9: 63-68.
3. Barrows, D. N. Am. J. Obst., 1927, 13: 710-719.
4. Bower, J. O., and Clark, J. H. Arch. Surg., 1925, 11: 586-597.
5. Broders, A. C. Minnesota M., 1925, 8: 726-730.
6. Doran, Alban. Tr. Path. Soc., Lond., 1888, 39: 208-217.
7. Idem. J. Obst. Gyn. Brit. Empire, 1910, 17: 1-23.
8. L'Esperance, Elise S. Proc. N. York Path. Soc., 1917, 17: 148-155.
9. Falk, E. Berl. klin. Wschr., 1898, 35: 554-556; 576-580.
10. Franqué, Otto von. Zschr. Geburtsh. Gyn., 1911, 69: 409-452.
11. Fullerton, W. D. Am. J. Surg., 1940 48: 467-472.
12. Holland, W. W. Surg. Gyn. Obst., 1930, 51: 683-691.
13. Kahn, M. E., and Norris, Samuel. Am. J. Obst., 1934, 28: 393-402.
14. Kaltenbach. Zbl. Gyn., 1889, 13: 74-75.
15. Le Count. E. R. Bull. Johns Hopkins, Hosp., 1901. 12: 55-68.
16. Martzloff, K. H. Am. J. Obst., 1940, 40: 804-817.
17. Mueller, Quoted by Barrows, D. N.(3).
18. Mullins, D. F., and Mosteller, R. Am. J. Obst., 1943, 45: 1042-1044.
19. Orthmann. Zschr. Geburtsh. Gyn., 1888, 15: 212-224.
20. Ries, Emil. J. Am. M. Ass., 1897, 28: 962-968.
21. Routier. Quoted by Holland, W. W.(12).
22. Smith, W. S. Am. J. Obst. 1932, 24: 267-270.
23. Stolz, Max. Arch. Gyn., 1902, 66: 365-412.
24. Stuebler, E., and Brandess, T. Quoted by Anspach, B. M.(1).
25. Thaler, H. Zbl. Gyn., 1920, 44: 576-579.
26. Tuffier. Quoted by Holland, W. W.(12).
27. Vest, C. W. Bull. Johns Hopkins Hosp., 1914, 25: 305-317.
28. Watkins, R. E., and Wilson, W. M. Surg. Gyn. Obst., 1930, 51: 125-131.
29. Wechsler, H. F. Arch. Path. Lab. M., 1926, 2: 161-205.
30. Wharton, L. R., and Krock F. H. Arch. Surg., 1929, 19: 848-870.
31. Wrork, D. H., and Broders, A. C. Am. J. Obst., 1942, 44: 412-432.

SPONTANEOUS RUPTURE OF THE SPLEEN

J. B. LITTLEFIELD, Sr., M.D., F.A.C.S., Lieutenant Colonel, M.C., A.U.S., Tucson, Arizona

SPONTANEOUS rupture of the spleen, a serious condition which demands careful clinical evaluation and prompt surgical intervention, is relatively uncommon and therefore may be difficult to diagnose. In the hope of stimulating interest in this subject 3 cases are presented to demonstrate this difficulty in diagnosis. Two of the cases are from personal experience and the third is reported from a clinical summary received from another hospital.

CASE 1. An enlisted man, 19 years old, was admitted to the hospital on August 17, 1943. He had served in the Army 4 months. His home was in Philadelphia, Pennsylvania. He complained of vague basal headaches, abdominal pains, and a cold. The headaches, which started soon after he was inducted into the Army, would last from 1 to 12 hours and would then disappear. He had rarely ever had a headache before induction. During these attacks his stomach was upset and he could not tolerate food. In addition he complained of shortness of breath. There was nothing significant in his past history. He was slender, 6 feet tall, and weighed 130 pounds. He had mild acne; his nose, nasopharynx, and tonsils showed a mildly acute infection. His chest and cardiovascular system were normal, the blood pressure being 110/64. The only positive findings were a generalized lymphadenopathy and an enlarged spleen. No abdominal tenderness was noted. Infectious mononucleosis was suspected and ruled out. The Wassermann test for syphilis was negative. The initial impression, as noted by the ward surgeon, was that the man was suffering from psychoneurosis and acute nasopharyngitis.

From August 17 until August 23, 1943, he ran a low grade temperature and developed a frank follicular tonsillitis. A course of sulfadiazine treatment, consisting of a total of 3 grams, was given during this period. The lymphadenopathy and enlarged spleen did not change perceptibly.

At approximately 11:30 o'clock on the morning of August 23, while returning from the latrine in the ward, he felt a sudden, severe pain in the upper left abdominal quadrant, became very weak, and barely managed to get on his bed, when he collapsed. He was seen immediately by the ward surgeon, who found him pale, cold, and clammy: his pulse was slow but weak. The blood pressure was 70 systolic and 40 diastolic. Tenderness was noted in the left lumbar region and over the spleen. His condition was that of typical hemorrhage and shock.

The intravenous administration of blood plasma was started immediately, and the foot of the bed was elevated. He was seen by the chief of the medical service in consultation, and we both felt that he was suffering from an intra-abdominal hemorrhage, most likely coming from the spleen. Five hundred cubic centimeters of citrated blood was given him. During the following 2 or 3 hours his blood pressure rose to 110/80, and the signs and symptoms of acute shock subsided.

In the interim, definite generalized tenderness developed over the abdomen, and we had the definite impression of shifting dullness in the abdomen on postural changes. The total red blood cells and hemoglobin decreased and the white cell count increased. At first there was a polynucleosis on differential count, but later we observed a definite reversal of the leucocyte-lymphocyte ratio (Table I).

At 8:30 p.m. we decided to operate, but the patient refused. Operation was therefore delayed until we could reach his father and mother in Philadelphia and obtain their consent to operate.

Pentothal sodium was given the patient while he was in bed, and this was supplemented in the operating room by ether administered by the closed method.

Operation was started at 1:03 a.m. and ended at 1:44 a.m. August 24, 1943. An incision approximately 7 inches long was made over the middle of the upper left rectus muscle, extending from the costoxiphoid angle to the level of the umbilicus. The abdomen was opened and a large quantity of dark blood was encountered. The spleen was found lying laterally against the abdominal wall. A large rent on its curved surface extended from the upper to the lower pole. It was delivered out of the abdomen and digital control was used on the pedicle until a series of clamps were applied. The pedicle was then divided and the spleen was removed. A mass ligature was placed around the pedicle, and each vessel was ligated separately distal to it. The raw surface was peritonealized. Several double handfuls of clots were removed from the left trough in the region of the left kidney. The abdomen was then closed without drainage. During the operation 500 cubic centimeters of citrated blood was given. He returned to his bed in excellent condition.

Following is the pathological report (Figs. 1 and 2): The specimen consists of a spleen immersed in normal saline, measuring 16 by 12 by 7 centimeters. On the diaphragmatic surface is a huge, gaping capsular rupture running the entire length of the spleen and measuring 8 centimeters across. This rent is covered by large, shaggy clots. Cut section shows indistinct markings. It is impossible to identify the follicles. The pulp is bright, pinkish red. The capsule is thin; the consistency very soft.

Microscopic examination revealed the following: The follicles are enlarged and not sharply demarcated. The pulp is cellular with increase in the monocytic elements. The sinusoids are collapsed and contain little blood. The capsule is thin. A laminated thrombosis covers the torn splenic surface.

Diagnosis: ruptured acutely hyperplastic spleen.

The postoperative course was very stormy and hectic. On the day following operation he was given a third transfusion of 500 cubic centimeters of citrated blood. From this time his red cells and hemoglobin stayed normal or above. Two days following surgery his temperature arose to 107 degrees F., but was easily controlled by covering him with a wet sheet and allowing an electric fan to blow on him. X-ray pictures at this time showed evidence of pneumonia in the left base. Treatment with sulfadiazine, 1 gram every 4 hours, was instituted. His temperature became normal 5 days after the operation. The sulfadiazine was discontinued the next day. On the following day a typical sulfadiazine rash appeared which desquamated as time went on.

On September 4, 1943, the wound separated down to the deep fascia. A course of treatment consisting of vitamins B and C followed.

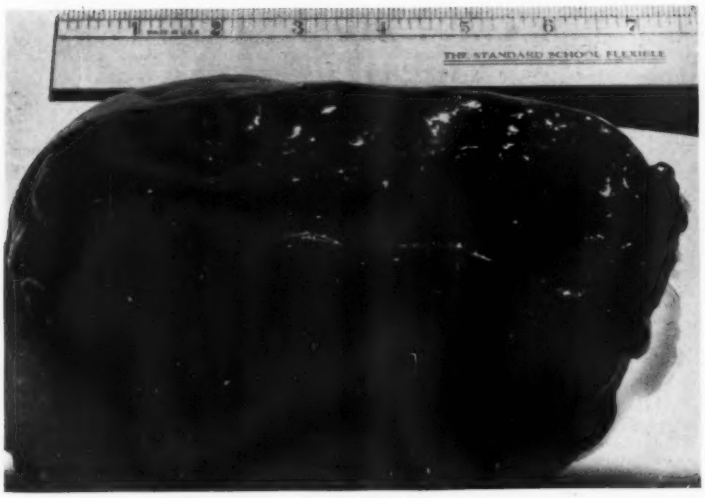


Fig. 1. Diaphragmatic surface of spleen.

Throughout September, 1943, there were episodes of low grade fever, anorexia, etc. Repeated examinations for undulant fever, malaria and the typhoid group were all negative.

During October he began eating better, gained weight and strength. He was transferred to the convalescent barracks. He began to complain of his basilar headaches and vague abdominal pains.

Finally, on December 9, 1943, he was given a certificate of disability discharge because of psychoneurosis, severe.

CASE 2. On November 25, 1943, an officer, aged 24 years, entered the hospital, complaining of soreness in his upper left abdomen and weakness. Ten days before entering the hospital, after doing a tumbling act at the gymnasium with other officers, he noticed a severe pain in the upper left quadrant of the abdomen, which was followed by diarrhea. The soreness persisted but he was constipated for 4 days. Diarrhea occurred again, followed by 3 days of constipation. The pain "feels like a steady cramp," he said. By this time our staff had become "ruptured spleen" conscious. When the attending surgeon secured this history and found an enlarged tender spleen, he immediately admitted him to the hospital. On admission his blood count was 3,900,000 red blood cells, 14,200 white blood cells, polymorphonuclears 81 per cent, and lymphocytes 19 per cent. A transfusion of 500 cubic centimeters of citrated blood was given.

He was observed carefully during the next 36 hours (7). During this time, in spite of the transfusion, his red blood cell count gradually fell. It was felt that the man was having a slow intra-abdominal hemorrhage, probably splenic in origin (1). The chief of the medical service and I were very much interested in the reversal of the leucocyte-lymphocyte ratio at this time (Table II).

TABLE I.—LEUCOCYTE-LYMPHOCYTE REVERSAL IN CASE I.

Date	Time	Rbc	Wbc	Hb gm.	Polys %	Lymphs %
8–18–44		4,500,000	10,600	14	71	29
8–23–44	10:00 a.m.	4,700,000	9,200		67	31
8–23–44	1:30 p.m.	Transfusion 500 c.c. citrated blood				
		4,300,000	24,800	13.5	43	57
8–23–44	7:30 p.m.	3,210,000	21,100	12	30	70
8–24–44	1:03 a.m.	Operation began		500 c.c. citrated blood		
	1:44 a.m.	Operation ended				
8–24–44	3:00 a.m.	3,000,000	18,300	10	32	68
8–24–44	Given 500 c.c. citrated blood					
8–25–44		3,900,000	18,500		69	36
		Given 500 c.c. citrated blood				
8–26–44		4,200,000	25,600	11	78	22
		Given 500 c.c. citrated blood				
8–28–44		4,950,000	16,400	13	70	30

After due consideration, operation was decided on, and was performed at 11:53 p.m. on November 26, 1943 (3).

Incision was made in the left paramedian line, extending from the costoxiphoid angle to the level of the umbilicus, thus opening the abdomen. There was slight evidence of hemorrhage present. A self-retaining retractor was placed in the wound. The anterior surface of the liver and gall bladder appeared normal. The abdominal contents were then gently pushed downward and to the right, exposing a very large spleen surrounded by free blood and blood clots. The dome of the spleen was found adherent to the diaphragm. These adhesions were broken down by blunt finger dissection. They were caused by an organized clot between the spleen and diaphragm. There was a small rent on the dome of the spleen, which was bleeding. After delivery of the spleen from the wound, blood was seen coming from the splenic vein in the hilus. Three clamps were applied to the pedicle and it was cut between the distal two. Double ligatures were placed on each vessel and the raw surface was peritonealized. All blood clots were removed from the splenic fossa. The liver and sur-

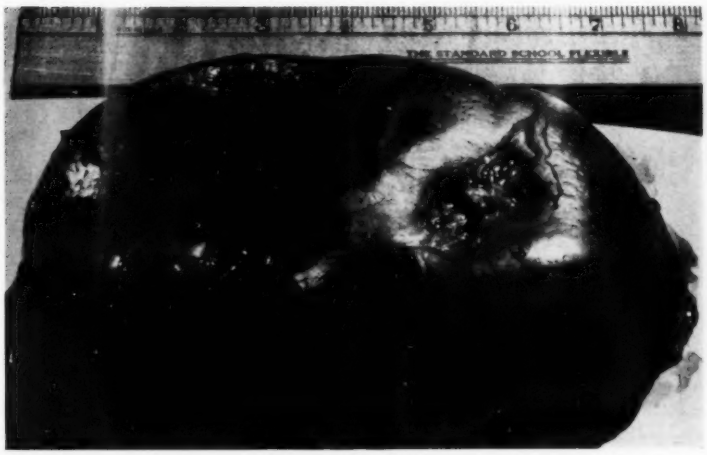


Fig. 2. Hilus of spleen.

rounding viscera were carefully examined for bleeding points, but none was found. The abdomen was closed and the patient was sent back to bed in excellent condition. Five hundred cubic centimeters of citrated blood was given during the operation.

Pathological report: The specimen consisted of a spleen immersed in formalin, measuring 18 by 11 by 8 centimeters. On the diaphragmatic surface near the upper pole a 20 by 8 millimeter firmly adherent dark red clot was seen which extended into the splenic substance for a distance of 4 millimeters as a sharply defined red area. On the anterior margin nearer the lower pole, two adjacent nodular 15 by 3 millimeter subscapular hemorrhages bulge slightly above the general level. On section they are sharply defined and dark bluish red. The splenic markings on cut section are indistinct and deep red.

Microscopic examination revealed the following: Two large subscapular hemorrhages were present. At another site the capsule was ruptured with a fragment lifted away over the blood clot with bands of fibrin. The follicles were indistinct. Both follicles and pulp were cellular. No abnormal cells were found. The sinusoids were congested with blood.

Diagnosis: ruptured hyperplastic spleen with hemorrhage.

We are not as sure about the pathological condition here as we were in the first case. There were both new blood and an organized clot about the spleen. The spleen was adherent to the diaphragm by an organized clot. The small tear seen in the capsule at operation and the bleeding from the splenic vein could have been more recent and due to handling. In view of the fact that no other hemorrhage was found and the patient's bleeding stopped following removal of the spleen, we are at a loss for any other explanation.

There is also a vague history of trauma here, whereas the other case was spontaneous on a basis of sepsis (6).

The postoperative course was stormy but not as bad as was the previous case. Wangensteen suction was used for 4 days.

On the tenth postoperative day, a friction rub developed at the base of the left lung. This was followed by pleural effusion. Aspiration had to be done approximately 35 days postoperatively. Following this the lungs cleared rather rapidly (Figs. 3 and 4). He was granted a sick leave of 30 days, 2 months following the splenectomy. On his return, his chest was negative and his blood picture was normal. He returned to full duty.

In the report of the Ninth Service Command for the week ending November 20, 1943, a case of spontaneous rupture of the spleen was recorded. We requested information from the hospital in which it occurred, and received a complete case report. The following is a brief résumé of the case:

TABLE II.—LEUCOCYTE-LYMPHOCYTE REVERSAL IN CASE 2

Date	Time	Rbc	Wbc	Hb-gm.	Polys %	Lymphs %
11–22–44	Out-patient	4,560,000	6,000	13	60	40
11–23–44	Admitted to hospital	3,900,000	14,200		81	19
11–25–44	Given 500 c.c. citrated blood					
11–26–44	9 a.m.	3,850,000	11,000	10	76	24
11–26–44	3 p.m.	3,700,000	10,000	10	78	22
11–26–44	8 p.m.	3,500,000	14,000	10.5	36	64
11–26–44	Operation 11:53 p.m.—ended 12:37 a.m. 11–27 Given 500 c.c. citrated blood					
11–27–44	....	3,680,000	19,000	11.5	45	55
12– 2–44	....	4,250,000	16,000	13	68	32

Fig. 3. Roentgenogram showing pleural effusion in left base.

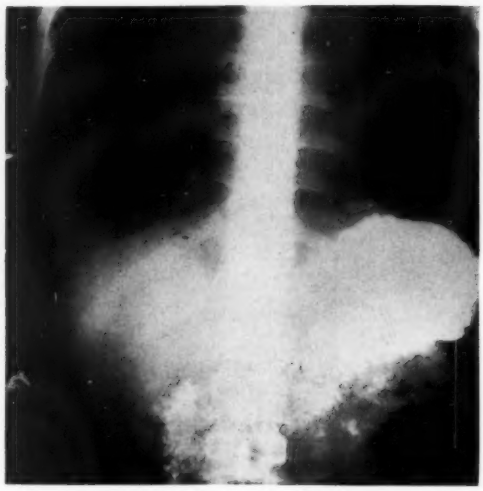


Fig. 4. Increased thickness in left diaphragmatic area after removal and absorption of pleural effusion.

CASE 3. An officer, aged 21 years, was admitted to the hospital November 4, 1943, at 9:00 p.m. He gave a history of feeling below par for 3 weeks. The only specific complaint was that of malaise and constipation. He had noticed transient abdominal pain on November 3, 1943, but continued to work. At 7:00 p.m., on November 4, 1943, two hours before admission to the hospital, he vomited several times, and had severe abdominal cramps.

On physical examination he was pale, his breathing was rapid, pulse 84, and his blood pressure was: systolic 90, diastolic 40. His heart tones were poor. He showed moderate abdominal distention, peristalsis could be heard, but no masses were palpable. There were no areas of localized tenderness.

X-ray picture of the chest was negative. His urine was normal and his blood count was: red blood cells, 3,680,000, white blood cells, 14,400, polymorphonuclears 84 per cent, and lymphocytes 16 per cent. He continued to grow weaker. At 1:00 p.m. on November 5, 1943, he was operated under spinal anesthesia. A very large, soft, friable spleen with many tears was removed. Two thousand cubic centimeters of blood and clots were removed. During the operation and immediately following it, he received 1000 cubic centimeters of plasma and 1000 cubic centimeters of citrated blood. At end of operation his blood pressure was 120/80 and his pulse rate was 120.

The pathological report follows: Specimen consists of a spleen which has been sectioned and partly crushed by being forced into a small bottle so that the external shape cannot be made out. The splenic tissue together weighs 470 grams. In some places the capsule is elevated by small blood clots. The splenic tissue is poorly fixed except just beneath the capsule where minute malpighian bodies can be made out. They are widely separated. The splenic pulp in the center of the organ is extremely soft, at least partly due to autolysis. Microscopic examination reveals marked diffuse cellular overgrowth of the pulp which widely separates the malpighian bodies and apparently infiltrates them at their periphery in most instances. Throughout the pulp there are seen numerous channels which are lined by endothelium. There is no evidence of increase in connective tissue. In the pulp there are seen a few plasma cells and rarely other mature leucocytes. The predominating cell is a fairly large, mononuclear cell with a deeply staining nucleus and in most instances a relatively small amount of cytoplasm. Some of these cells have larger amounts of cytoplasm and distinct cell outlines. There are frequent mitotic figures and many of the immature cells show fairly prominent nucleoli. Reticulum stains of the spleen show a slight variation in the amount of reticulum in different portions of the spleen: however, there is no great increase and it is questionable whether there is any increase in reticulum. A relatively small number of the cells are surrounded by reticulum.

Impression: reticulum cell sarcoma of spleen.

By November 7, 1943, he had developed pneumonia in the left base and was placed in an oxygen tent. He was given sulfadiazine and other supportive treatment. Twelve days after operation after a severe coughing spell, the wound separated. This was closed under pentothal anesthesia. He never rallied and died in spite of all supportive measures.

At autopsy the following findings were recorded: (1) pneumonia, lobar, lower lobe left, upper and lower lobes right; (2) pleurisy, acute, serofibrinous with effusion, left, severe, secondary to lobar pneumonia; (3) embolism, organized thrombus, right pulmonary artery, severe, probably secondary to lobar pneumonia; (4) surgical absence of spleen.

SUMMARY AND CONCLUSIONS

1. Spontaneous ruptures (4) occur in the soft, overdistended spleen of acute fevers, like malaria, typhoid, typhus, acute septic splenitis and infectious mononucleosis. A rupture is said to be spontaneous (2) when it happens without apparent trauma, or after the insignificant trauma of muscular exertion.

2. The 2 original cases of this report showed a reversal in the leucocyte-lymphocyte ratio before surgery which corrected itself soon after surgery

(Tables I and II). In the last edition of *Physiological Bases of Medical Practice*, by Best and Taylor, the statement is made: "The spleen serves three well recognized purposes, namely: (1) the final destruction of blood cells, (2) the storage of blood and (3) the manufacture of lymphocytes in the lymphoid tissue composing the malpighian corpuscles." Immediately after operation there is usually a leucocytosis reaching as high as 30,000. At first the polymorphonuclears predominate, but as the total count approaches normal there is usually a reversal and the lymphocytes predominate. Klemperer and Hirschfeld suggested that this action might be accounted for by removal of an organ where pressure, possibly hormonal, exercised a depressant action on the bone marrow. Bertelli, Falta and Sweeger point out that the changes in the peripheral blood may also be brought about by the injection of substances which increase the tone of the autonomic or of the sympathetic nerves. Careful review of available literature did not reveal an instance of this reversal being recorded in a case of a bleeding ruptured spleen before its removal. In both of our cases, repeated blood counts were made, and the hemorrhage was sufficiently slow to permit this change before surgery.

3. Each of the 3 cases mentioned developed pleural and pulmonary complications. It started as pleurisy in the left base. In the second case, pleurisy with effusion predominated. Since the curved side of the spleen is against the diaphragm on the left side, the irritation from the hemorrhage and from the trauma of the surgery causes a splinting of the diaphragm, which invites stasis and localized atelectasis in the base of the left lung, thus bringing about pneumonitis and pleurisy (Figs. 3 and 4).

4. Two of the patients had wound separation. In both of these the chest complications came on early, with coughing. In the second case the chest complications manifested themselves after the wound had healed, and the coughing did not disrupt the incision.

5. Embolism is a very common complication. It was probably the immediate cause of death in the third case report.

The splenic veins frequently became thrombosed. Since the splenic and the superior mesenteric veins unite to form the portal vein, embolism may give rise to septic pylephlebitis of the liver (5).

REFERENCES

1. Blocker, T. A., Jr. Texas J. M., 1939, 34: 478-483.
2. Briner Osborne A. Arch. Path., 1943, 36: 163-166.
3. Cole, W. H. Surg. Clin. N. America, 1942, 22: 43-62.
4. Dubasch, Jal, and Langley, G. F. Brit. M. J., 1944, 1: 183–184.
5. Gius, John A., McGovern, John P., and McMurray, W. B., Jr. Ann. Surg., 1945, 121: 100-110.
6. Puestow, C. B. Surg. Clin. N. America, 1940, 20: 195-205.
7. Zabinsky, Edward J., and Harkin, Henry N. Arch. Surg., 1943 46: 186-213.

ACCIDENTAL TRANSPLANTATION OF CANCER IN THE OPERATING ROOM

With a Case Report

W. W. BRANDES, M.D., W. C. WHITE, M.D., F.A.C.S., and J. B. SUTTON, M.D.,
New York, New York

THE literature contains many references to local recurrence, about the operative site, of cancer of the breast and of other organs. Ryall (3), nearly 40 years ago, pointed out that recurrence was frequently due to contamination of the instruments used in operation with the cells from the tumor being removed. He cited a series of cases in which cancer of the breast, tongue, lip, larynx, rectum, and colon were reimplanted at the operative sites through "cancer infection" of the wounds by contaminated knives and needles. He mentioned the postoperative occurrence of a "distant" nodule in the axillary fold following a radical mastectomy, when a stab wound for drainage of the operative site was made with the knife which had been used in the mastectomy, and concluded that it was "therefore of the utmost importance to guard against the danger of implanting these cells into any fresh wound." In 1908(4), he recommended a complete change of gloves, drapes, and instruments, and repreparation of the operative site after biopsy of a malignant tumor has been completed and the exploratory incision closed. This recommendation has been made repeatedly since then, having been especially emphasized by Ewing in 1933 and by Saphir in 1936.

Saphir presented objective evidence of the presence of viable tumor cells on knives used for biopsies; he made smears directly from knife blades and from saline in which such blades had been rinsed. He found large numbers of tumor cells on blades used to incise tumor masses, and on those used to remove the tumors for biopsy prior to radical mastectomy. He demonstrated the viability of the cells by means of supravital staining, according to the method described by Hickling. Thus, the presence on instruments of tumor cells, viable and capable of transmitting the "cancer infection" to other parts of the operative wound, which for many years had been assumed, was clearly demonstrated.

From the Departments of Pathology and Surgery, The Roosevelt Hospital, New York.

Tumor growth is occasionally seen at the site of paracentesis or thoracentesis wounds in carcinomatosis of the peritoneum or pleura. We have seen this in 2 instances in the past 2 years.

The operators' gloves must obviously be another convenient means of transfer of tumor cells, and we wish to report here a case in which it seems evident that contamination of the gloves was responsible for transplantation of a highly malignant carcinoma of the breast from the mastectomy site to a skin donor area on the left thigh. We have seen no previous report of transfer to so distant a site.

CASE REPORT

Mrs. M.W., a 47 year old office receptionist, entered The Roosevelt Hospital on May 19, 1944, as a patient of Dr. W.C. White. Ten months previously she had noticed a small lump in her right breast, which had grown slowly. More recently, her doctor had discovered axillary nodes.

Physical examination revealed a 2.5 centimeter, nontender lump in the right breast, situated at "2 o'clock," about 4 centimeters from the nipple. Its mobility was slightly limited, but it was not actually fixed; it gave the impression of being attached to the underlying fatty tissue but not to the fascia. There was a faint trace of dimpling of the skin over the tumor on movement. Three hard, nontender, freely movable lymph nodes could be felt in the right axilla, and smaller firm nodes were found in the left axilla and in the right supraclavicular region.

On the second hospital day a radical mastectomy was performed, with immediate skin grafting.

A radial incision was made over the tumor, which, together with a generous amount of surrounding fatty tissue, was excised with the high frequency needle. The tumor itself was not incised. Frozen section revealed carcinoma. The biopsy wound was closed with silk and the patient was redraped, the operative area having been painted again with merthiolate. The operator, his assistants, and the instrument nurses changed to fresh gloves and gowns, and another set of instruments was substituted for those used in excising the tumor. A circular incision was then made about the tumor site with a radius of about 2½ inches, in order to avoid incising or approaching the tumor site. The wound was extended obliquely down toward the abdomen, after which the nipple, skin, breast tissue, thoracic portion of the pectoralis major and the pectoralis minor, and the axillary contents from the apex of the axilla, downward and outward, were removed. The wound edges were sutured to the chest wall, leaving a raw area, irregular in outline and measuring roughly 7 by 10 centimeters. A Padgett skin

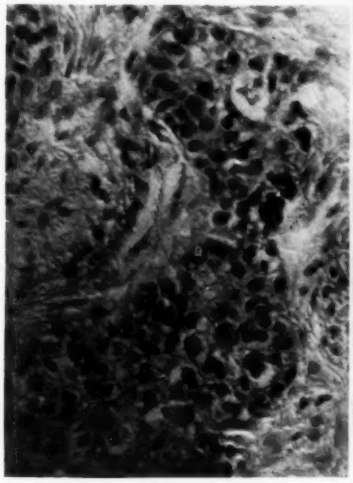


Fig. 1.

Fig. 2.

Fig. 1. Primary growth in the breast. Grade III malignancy. Hematoxylin and eosin. ×288.6.

Fig. 2. Section of transplanted tumor nodule on left thigh. Skin surface visible at upper left. Hematoxylin and eosin. ×96.

Fig. 3.

Fig. 4.

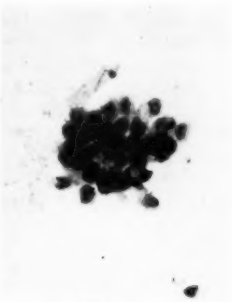


Fig. 5.

Fig. 3. Clump of tumor cells and lymphocytes found in sediment of washing fluid from operating room. Hematoxylin and eosin. ×322.6.

Fig. 4. Tumor cells in operating room fluid. Case of carcinoma of the breast. Tumor mass was not incised by the operator. Distilled water. Hematoxylin and eosin. ×322.6.

Fig. 5. Tumor cells in saline from operating room basins. Same case as in Figure 4. Hematoxylin and eosin. ×322.6.

graft, .008 inch in thickness, was then removed with a dermatome from a previously prepared donor site on the left thigh, and the graft was sutured to the wound edges with interrupted silk, punctured in many places, and dressed with a cellulose sponge for pressure. The donor area was dressed in a similar manner.

After the mastectomy, and before the skin grafting was done, the operator's and assistants' gloves were washed in distilled water, but were not changed.

Pathological examination of the tissue showed a tumor mass measuring 3 by 3.5 centimeters, irregular in outline, unencapsulated, and extending into the surrounding fatty tissue. Diagnosis was scirrhous carcinoma of the breast, grade III, with metastatic involvement of axillary lymph nodes (Fig. 1). Neither the tumor mass nor the involved nodes had been directly incised by the operator.

During a rather slow postoperative recovery, additional nodes were removed from the posterior triangle of the neck on the right side, and on examination, these also revealed metastatic carcinoma. Epithelization of the donor site on the thigh was slow, and the patient's general condition did not warrant discharge from the hospital until the 8th postoperative week. X-ray examination of the chest, made just before discharge, was negative.

One month later the patient was readmitted in a state of cachexia. X-ray studies at this time showed widespread metastatic involvement of lungs and bones, and there were local skin recurrences at the mastectomy site. Her course was rapidly downhill, and she died on the 32nd hospital day.

At autopsy, the patient was pale, cachectic, weighing about 100 pounds. Multiple skin recurrences were noted along the mastectomy scar, at the lines of incision and at the sites of suture wounds. Multiple metastases were seen throughout the chest cavity, particularly on the right; the right pleura, lung, pericardium, and mediastinal nodes were involved, and there was a nodule on the wall of the right auricle.

The skin donor site on the left anterior thigh was studded with firm, discrete, irregular nodules, the largest being about 0.5 centimeter in diameter (Fig. 2). Microscopic examination of these nodules revealed carcinoma similar to that seen in the primary breast tumor (Fig. 2).

The possibility of metastatic transfer by way of the blood or lymph stream from the breast to the skin of the thigh is too remote to be considered, and since no instruments were used both at the breast site and at the donor area, the gloves of the operator and his assistants must obviously have been the means of transfer of tumor cells. We have previously pointed out that the gloves were washed in the basins of distilled water provided in the operating room for that purpose, after the mastectomy and before the removal of the dermatome graft from the thigh. Merely washing the gloves in this manner is obviously an insufficient precaution; the tumor cells may not be completely removed from the gloves, and in any event the washing fluid is contaminated with them. The gloves, still wet with this fluid, must thus be assumed to be contaminated.

We have centrifuged the contents of such basins, the fluid having a volume of 2½ to 3 liters, and have found well preserved tumor cells in the sediment. It is not necessary that the tumor be handled deliberately. In 1 instance, easily identifiable tumor cells were demonstrated in the fluid after a radical dissection of the right inguinal region for removal of tumor-bearing inguinal nodes (Fig. 3); the primary tumor, a poorly differentiated squamous cell carcinoma, had previously been removed from the dorsum of the foot, between the toes. Since the nodes were not incised, the contamination must have resulted from the opening of involved lymph channels, which, obviously, cannot be avoided. The accidental transfer of malignant tumor cells from an operative site to a distant part of the body can be avoided by changing gloves and avoiding the use of contaminated washing fluid, after the tumor-bearing area has been handled.

Cells have also been found in a number of cases in the fluid used during operation for carcinoma of the breast (Figs. 4 and 5). In cases in which the tumor has been handled directly and incised, the cells are more abundant, as is to be expected. When distilled water was used, it was necessary to centrifuge the fluid and make the smears rather soon after the washing, in order to obtain well preserved cells. Cells left in distilled water for more than about 30 minutes before the fluid is centrifuged often become swollen and even disintegrated; such cells are probably nonviable. Even with distilled water, however, it should be possible to transfer viable cells when repeated washing of gloves is done at short intervals, when more than one operator uses the same basin, or when gloves are changed and the fluid used to wash the original gloves is again used to remove powder from the new pair before returning to the operation. When normal saline is used, cells apparently remain viable for longer periods.

We have had no difficulty in verifying and repeating the work of Saphir. Tumor cells were demonstrated not only on the blades of knives used in resection or biopsy of malignant neoplasms, but on clamps and tenacula used to grasp breast tumors or to catch bleeding vessels adjacent to them.

SUMMARY

A case is reported in which, several months after a radical mastectomy for a highly malignant scirrhous carcinoma of the breast, cancer nodules were found in the skin of the donor site on the opposite thigh. The usual precautions had been taken after biopsy of the tumor and before the mastectomy, viz., changing of operators' and nurses' gloves, and redraping and repreparation of the patient. However, after the mastectomy, when a defect in the skin over the operative site was to be covered, a skin graft was taken from the left anterior thigh without first changing the contaminated gloves used at operation. Washing the gloves in sterile distilled water was apparently insufficient, and tumor cells were transferred from the operative site to the raw donor area, where they survived and gave rise to tumor nodules.

Previous work in which tumor cells have been demonstrated on knives used for biopsies is reviewed, and it is also shown that the fluid customarily used in the operating room to wash the gloves of the operators is another potential source of contamination of distant parts with malignant tissue.

REFERENCES

1. Ewing, J. Illinois M.J., 1933, 63: 482.
2. Hickling, R.A. J. Path., Bact., Lond., 1931, 34: 789.
3. Ryall, C. Lancet, 1907, 2: 1311
4. Idem. Brit. M.J., 1908, 2: 1005.
5. Saphir, O. Surg. Gyn. Obst., 1936, 63: 775.

INTERCORPORAL BONE GRAFT IN SPINAL FUSION AFTER DISC REMOVAL

IRWIN A. JASLOW, M.D., Sayre, Pennsylvania

FUSION of the adjacent vertebrae following the removal of degenerated discs is gradually being accepted as the proper procedure. In clinics where simple removal of the disc without fusion is performed, the results are poorer than in those where the combined procedures are done. Due to this fact, many more fusions are now being performed. Frequently patients who did not have fusions initially have returned for secondary fusions because of persistent low back pain, long after the sciatic radiation had been relieved by removal of the degenerated and protruded disc. Other undesirable sequellae following disc removal without fusion have been illustrated in a recent paper by Graf and Hamby.

On both a theoretical and practical basis, fusion is indicated. Theoretically, fusion should be performed because the low back pain which antedates the onset of radiating pain to the buttock or leg by months or years in the majority of cases indicates an instability in the lower spine. In addition, there are multiple anomalous developments of facets of the fifth lumbar vertebra, and to a lesser degree the fourth. Their asymmetry and the fact that they are the last and most vulnerable movable segments attached to the pelvis indicate the desirability of fusion. These are the factors which seem to cause the high incidence of degeneration of intervertebral discs at these levels, eventually resulting in protrusion and pressure on nerve roots. We can recall many patients who were completely relieved of their symptoms by simple fusion done after a diagnosis of "unstable fifth lumbar vertebra" was made, with or without "sciatic scoliosis." The latter we now know as a protective list. A review of the histories and physical findings in many of these patients reveals data identical with that of patients whom we now know to have sciatica from disc pressure. It can be assumed, since they were completely and permanently relieved without removal of the disc, that they could have had incompletely protruded discs or discs which caused nerve root pressure only in certain positions. At operation or in bed following the fusion, such discs probably returned to their normal positions and after fusion took place between the vertebral laminae were incarcerated in the disc space. Without intervertebral motion, they could not protrude again.

It has been stated in some quarters that a fusion operation in itself is unnecessary, since thorough curettage of the disc space will allow the vertebral bodies to fuse. The proof for such a statement is lacking, and vertebral fusion has been rarely demonstrated except in a few cases complicated by infection. The removal of the intervertebral disc and cartilage leaves a space between the vertebral bodies, the ideal situation for nonunion. The writer has had the opportunity to see several patients who came to fusion after discs had been removed elsewhere. In all of these cases, motion between the adjacent vertebrae was readily demonstrated by pressure on the spinous processes at the time of operation.

This paper is a description of an adjunct to spinal fusion after disc removal.[1] A peg of bone is driven in between the vertebral bodies into the space from which the degenerated disc and cartilage plates have been removed. It is felt that this peg serves several useful functions: (1) It maintains the height of the disc space so that there will be no pinching of the nerve roots in the intervertebral foramina. Indeed, in several cases in which the preoperative films revealed narrow disc spaces, the postoperative films taken 6 weeks later revealed definite widening of the involved spaces. (2) The space left by removal of disc and cartilage is partially taken up by the peg so that there is no distraction, and the space that would ordinarily be filled with blood clot and eventually fibrous tissue is partially taken up by an osteogenic bone graft. These factors tend to promote bony union between vertebral bodies. (3) The placing of the peg into the intervertebral space under forced flexion provides increased stability which allows earlier mobilization of the patient, without fear of pseudarthrosis.

Operative procedure (Fig. 1). With the patient lying prone and the lumbar spine flexed acutely,

From the Section on Orthopedic and Traumatic Surgery, Guthrie Clinic and Robert Packer Hospital, Sayre, Pennsylvania.

[1] The idea for the use of the bone peg was the result of a discussion with Dr. Henry Briggs of East Orange, New Jersey. It was under his supervision that the first bone peg was inserted in 1943, at the New Jersey Orthopaedic Hospital.

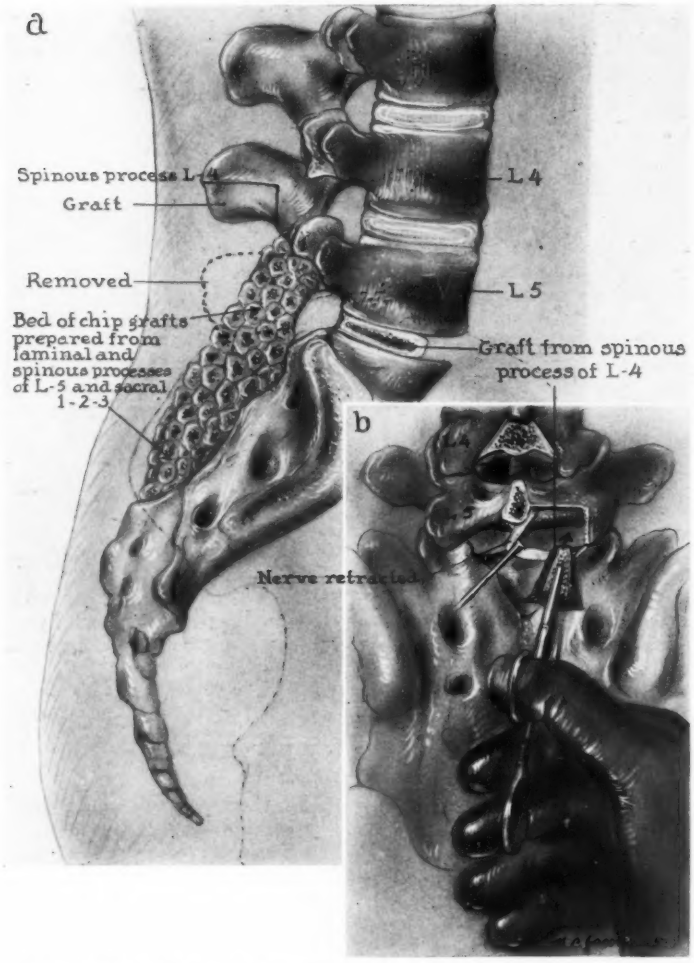


Fig. 1. a, The position of the intercorporal bone graft is shown, along with the posterior fusion mass. b, The manner in which the graft is inserted is demonstrated, diagrammatically. (The nerve root is not retracted quite so vigorously at operation.)

the lumbosacral spine is exposed subperiosteally through a midline incision from the third or fourth lumbar level to the level of the spinous process of the third sacral segment and laterally to the facets. A self-retaining retractor is placed. For the exposure of the fifth lumbar disc, the spinous processes of the fifth lumbar and the upper sacrum are removed flush with the lamina with an osteotome or heavy rongeur forceps. Ligamentum flavum and enough bone to permit the passage of a finger tip are removed from the affected side of the interlaminar space to reveal the bulging or herniated disc pressing on the first sacral nerve root. If the disc appears normal and no nerve pressure is demonstrated, the fourth lumbar disc is explored in similar fashion and the spinous process of the fourth lumbar vertebra removed. When the disc causing nerve root pressure is found, it is removed with a pituitary rongeur, either through the hole in the annulus fibrosus through which it ruptured in the case of the herniated disc, or through a hole cut in the

Fig. 2. The bone graft in position in the fifth lumbar disc space, 6 weeks postoperatively.

Fig. 3. The bone graft in position in the third lumbar disc space, 3 weeks postoperatively. The posterior fusion mass between the third and fourth lumbar vertebrae is well demonstrated. (In this case pantopaque myelography was performed because of bizarre neurological findings indicating that the lesion was not at the fifth or fourth lumbar disc. About two-thirds of the pantopaque was removed.)

annulus fibrosus in the cases of the bulging and hidden discs. The disc space is then thoroughly curetted to remove the remaining disc material and cartilage plates of the vertebral bodies. Care is taken to stay within the intervertebral space.

A rectangular peg is fashioned from the spinous process of the vertebra above. This is usually about 2 centimeters long and slightly higher than the estimated disc space. By levering on the adjacent lamina the former disc space is widened enough to allow this peg to be inserted into place. It is then rotated 90 degrees by means of a small curet so that the long axis is broadside to the hole in the annulus fibrosus through which it was placed. This diminishes the possibility of its being pushed back into the spinal canal. In the more recent cases, up to four pegs have been placed in the same disc space. The exposed nerve root which was retracted medially is allowed to return to its normal position and is covered with a piece of subcutaneous fat. Muscle or a thrombin coated absorbable starch sponge is used in troublesome hemorrhage.

A modified Hibbs or chip fusion is now performed. The facets are thoroughly curetted free of cartilage, and bone chips are turned into the apophyseal joints. The laminae of the most superior vertebra to be fused are turned up cephalad in the form of a buttress. More bone chips are cut from the laminae of the caudal vertebrae with a gouge until no cortical bone is visible on the upper sacral and lumbar laminae to be fused. To these chips are added others cut from the previously removed spinous processes.

After wound closure, the patient is placed in a firm bed without other support. He is allowed up in 3 to 6 weeks, usually with a light brace or canvas support. In recent months, 2 patients have left the hospital without brace support, because they were unwilling to wear one; they have suffered no ill effects, and follow-up roentgenograms demonstrate satisfactory progression toward fusion.

Since the procedure described has been in use for only 2 years, no attempt is made to evaluate

end-results except to state that none of 27 patients has complained of low back pain and none has had recurrence of sciatica. It is described as a logical method in attempting to obtain vertebral body fusion. It increases stability while posterior fusion is taking place and maintains or increases the height of the disc space. The procedure adds only a few minutes operating time to the ordinary combined operation and no untoward effects have been observed. Lateral roentgenograms demonstrating the osseous peg are shown in Figures 2 and 3.

SUMMARY

An operative technique which adds stability to a localized low back fusion following excision of lower lumbar intervertebral discs is described. Patients become ambulatory relatively early following operation. Follow-up examination shows by roentgenogram that adequate fusion has taken place and that the *patients are relieved of both low back pain and sciatica.*

REFERENCES

1. Bradford, F. K. South. Surgeon, 1941, 10: 623.
2. Idem. U. S. Nav. M. Bull., 1944, 42: 763.
3. Briggs, H., and Milligan, P. R. J. Bone Surg., 1945, 26: 125.
4. Craig, W. M. Am. J. Surg., 1939, 45: 499.
5. Dandy, W. E. J. Am. M. Ass., 1942, 120: 605.
6. Idem. Ann. Surg., 1943, 118: 639.
7. Ibid., 1944, 119: 481.
8. Graf, C. J., and Hamby, W. B. Am. J. Roentg., 1945, 53: 157.
9. Keegan, J. J. J. Bone Surg., 1944, 26: 238.
10. Mixter, W. J. Ann. Surg., 1937, 106: 777.
11. Mixter, W. J., and Barr, J. S. N. England J. M., 1934, 211: 210.
12. Petter, C. K. J. Bone Surg., 1933, 15: 365.
13. Smith, A. D. F., Deery, E. M., and Hagman, G. L. J. Bone Surg., 1944, 26: 821.
14. Spurling, R. G., and Cranthам, E. G. Arch. Surg., 1940, 40: 375.
15. Spurling, R. G., and Thompson, T. C. Surgery, 1944, 15: 387.

THE INITIAL SURGICAL TREATMENT OF PENETRATING WOUNDS OF THE RECTUM

HAROLD LAUFMAN, M.D., F.A.C.S., Major, M.C., A.U.S., Chicago, Illinois

THIS communication is based upon a series of 35 consecutive cases of penetrating wounds of the extraperitoneal portion of the rectum operated on at an Evacuation Hospital during the Italian campaign. Its purpose is to emphasize certain phases of the diagnosis, anatomy, and surgical treatment of these wounds, and to pose some questions relative to factors governing their management.

Missiles entering the body anywhere between the levels of the lower thigh and the costal margin have been known to penetrate the rectum. This is especially true of wounds of the dorsal surface of the body. Wounds of the buttocks, hip area, sacral area, and posterior thighs are extremely common in warfare because of the prone position a soldier usually assumes while under fire. While wounds of these regions are most likely to involve the rectum, the incidence of rectal penetrations, fortunately, is relatively very low. In our experience, only 6 per cent of buttock wounds penetrated the rectum. Because of its protected anatomical location, the rectum will usually escape injury unless the missile has crossed or has lodged near the midline.

The patient with a penetration of the extraperitoneal portion of the rectum may present no symptoms referable to this organ at the time of initial examination. Consequently, unless a thorough appraisal of the case is made prior to surgery the lesion may be overlooked. It is important to study the pathway of the missile by inquiring into the position of the patient at the time of injury and by careful examination. It hardly seems necessary to emphasize the warning that in studying roentgenograms one must make sure of right and left sides. Yet it is easy to assume that a foreign body lies on the same side as the wound of entrance, unless this point is checked. When roentgenological evidence indicates that a pelvic foreign body has traversed the midline, suspicion should be directed immediately toward the possibility of rectal injury. When no foreign body is demonstrable in the films, reexamination of the patient is imperative to ascertain the location of the wounds of entrance and exit, and to reconstruct the possible course of the missile. In one of our patients a shell fragment had entered the body above the left iliac crest, perforated the rectum, and emerged on the lateral aspect of the lower third of the right thigh. From the appearance of the wounds they seemed to be two completely unrelated, penetrating wounds.

What often appears to be an innocuous wound of the buttock or thigh, not infrequently is found to penetrate the rectum. The same warning has been made repeatedly in regard to wounds which penetrate the abdominal cavity via the buttocks, and has resulted in routine abdominal examinations of patients with buttock wounds. However, in the event that the abdominal cavity does not appear to be penetrated, the possibility of rectal injury should not be overlooked before relegating the case to a low priority on the operative schedule during a rush period.

It is as important not to overlook concomitant injuries as it is to search for rectal injury. The urinary tract is investigated by physical examination for urinary extravasation, by catheterization and by urinalysis. It has been our policy to carry out this procedure in every case of injury about the pelvis. The possibility of peritoneal penetration and major vascular injury is the object of careful routine examination.

On the other hand, the presence of other, apparently more urgent wounds should not be allowed to divert the attention of the examiner away from the possibility of rectal injury. Wounds with dominating symptoms which are most likely to coexist with penetrations of the rectum and thereby lead to incomplete investigation of a rectal injury are: (1) penetrations of the peritoneal cavity from wounds in the groins, hip area, sacral area, buttocks or posterior thighs; (2) wounds involving the urinary bladder or urethra; (3) wounds involving the major vessels of the upper thighs and pelvis; (4) wounds involving the sciatic nerve; (5) wounds involving the spinal cord; (6) wounds resulting in compound fractures of the pelvis, sacrum or femur.

Gordon-Watson relates a bizarre experience with a patient with a bullet wound of the greater trochanter. A wound of the rectum was not suspected "until the patient passed wind through the greater trochanter with a high musical note."

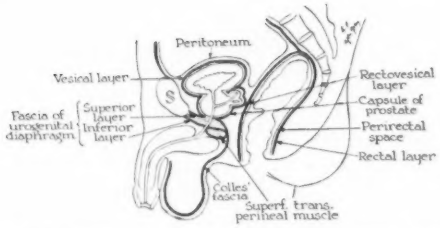


Fig. 1. Diagrammatic representation of sagittal section of pelvis showing distribution of endopelvic fascia and planes along which infection can travel rectal wounds.

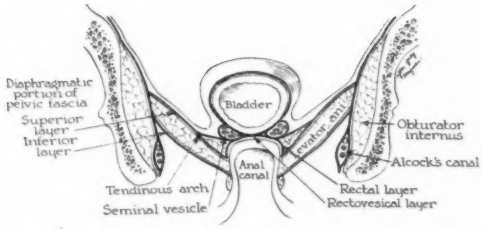


Fig. 2. Diagrammatic representation of coronal section of pelvis viewed from behind showing further distribution of endopelvic fascia.

In our series there was a patient who was placed in the hands of the urosurgeons when the preoperative medical officer discovered that a wound in the groin had penetrated the patient's urinary bladder. This diagnosis was evident from the presence of gross blood in the urine. The wound of exit was in the perineum, lateral and anterior to the anus. After the suprapubic cystotomy had been done, a rectal examination showed blood on the gloved finger. A re-examination of the patient revealed that fragmentation of the missile occurred after it entered the body; that although there was only one wound of entrance, some fragments penetrated the urinary bladder while others found an exit posteriorly. Proctoscopic examination revealed no less than four small perforations of the extraperitoneal portion of the rectum. A second operation consisting of posterior drainage and sigmoid colostomy was done. Although the patient made an uneventful recovery, it is obvious that it would have been preferable to have had a complete appraisal of the nature of the injury prior to initial surgery, so that the complete operation could have been done at one time and so that the patient would not have had to undergo two periods of anesthesia.

Another patient was operated on for multiple penetrating and perforating wounds of both thighs, legs, and feet, with a compound fracture of one foot, and a penetrating wound of the buttock. All the wounds were severe. The missile which entered the buttock caused a compound fracture of the ilium, and, though it crossed the midline, apparently passed superficial to the coccyx, missing the rectum. The latter conclusion was based on digital examination and following the tract at operation. After a lengthy operation consisting of débridement of all the wounds and immobilization of the limbs in plaster, the surgeon was not altogether satisfied that the rectum was intact, but postponed proctoscopy until the next day. This examination revealed a tear in the posterior wall and the patient had to undergo a second operation. Here too, it would have been preferable to have done the proctoscopic examination before surgery, and to have performed the entire operation at one time. The length of operating time need not necessarily have been greatly increased, since a second team of surgeons could have been employed to work simultaneously on the limbs.

Digital examination of the rectum is very helpful in most cases. But when the perforations are small and the mucosa has contracted partially to seal them, the examining finger often comes away with no blood. Nor can all perforations be palpated. It is also important not to be misled by allowing blood from the perianal skin on the gloved finger to be interpreted as coming from within the canal. Palpation of a foreign body through the rectal wall does not necessarily mean that the mucosa has been breached. Yet, it is imperative to know whether the mucosa is intact or not, since if it is, nothing more than débridement and posterior drainage of the wound need be done, while if it is not intact, a more extensive procedure may be necessary, such as colostomy.

The most important diagnostic criterion for the determination of the presence of rectal perforation when palpation fails to disclose the perforation, is direct vision by proctoscopy. This can often be done on the operating table while the patient is being prepared, if it has not already been done in the preoperative department, and consumes no additional time. Only by proctoscopy can the nature and extent of the penetrations be ascertained.

The reason for emphasizing a painstaking search for rectal penetrations is based on the fact that if they are discovered and adequately treated, one need not fear the development of serious complications from infection. The pertinent anatomy must be understood to appreciate this point (Figs. 1 and 2).

When a breach in the rectal mucosa is repeatedly contaminated from intraluminal contents, the spread of infection takes place along fascial planes.

The fascia of the pelvis is reflected over the muscular structures and over the pelvic viscera, so that it is commonly resolved into: (a) the fascial sheaths of the obturator internus muscle, the piriformis, and the pelvic diaphragm; (b) the fascia associated with the pelvic viscera, known as the endopelvic part of the pelvic fascia, or simply as the endopelvic fascia (2).

The endopelvic fascia is reflected over the various pelvic viscera to form fibrous coverings for them. It is attached to the diaphragmatic part of the pelvic fascia along the tendinous arch, and has been subdivided in accordance with the viscera to which it is related. Thus, its anterior part, known as the vesical layer, forms the anterior and lateral ligaments of the bladder. Its middle part crosses the floor of the pelvis between the rectum and seminal vesicles as the rectovesical layer. Its posterior portion passes around the rectum, forming for it a loose sheath, which is, however, firmly attached around the anal canal. This sheath is known as the rectal layer of the endopelvic fascia. By common usage the name "fascia propria" of the rectum has been applied to this part of the endopelvic fascia. Actually, it does not belong to the mural structures of the rectum, but, as has been pointed out, is part of the endopelvic fascia covering this organ.

The abdominal counterpart of the endopelvic fascia is the endoabdominal fascia (transversalis fascia) which encases the abdominal cavity on all sides. In fact, the endopelvic and endoabdominal fascias fuse at the upper border of the obturator internus muscle and have been described as one and the same layer. Analogous to the layer of fat containing blood vessels (properitoneal fat; retroperitoneal fat) which lies deep to the endoabdominal fascia, is the pelvic layer of fat containing blood vessels, which lies deep to the endopelvic fascia. In the pelvis, where peritoneum does not exist, this layer of fat lies directly upon the pelvic viscera, serving as a protective layer for the blood vessels nourishing these organs. The portion of this fatty layer which surrounds the bladder is known as prevesical fat. The portion which surrounds the rectum is less well known, but can be clearly demonstrated, especially in well nourished young adults, and can be termed prerectal or perirectal fat. The only barrier between the perirectal fat and the lumen of the rectum consists of the coats of rectum itself, namely, the longitudinal and circular muscular coats, the areolar coat (tela submucosa) which connects the muscular and mucous layers closely together, and the mucous membrane.

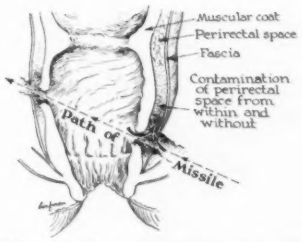


Fig. 3. Diagram of coronal section of rectum showing mode of contamination of perirectal space from within and without. Width of perirectal space exaggerated.

With this anatomical picture in mind, the path of bacterial invasion from the rectal lumen via a wound in the rectal wall is evident. Bacterial contamination from an active fecal current can pass through the injured rectal wall and attack the susceptible fat (Fig. 3). Without an adequate opening in the rectal portion of the endopelvic fascia, this layer of fat is placed under pressure and rapidly breaks down. Since most penetrating wounds of the rectum have long tracts from the point of entry on the skin to the lumen, the various layers of muscle and fascia of the buttock, thigh or back, whichever the case may be, slide to form trap doors at each tissue plane. Thus, the escape of infected material is blocked even in cases in which the missile tears a gaping hole in the rectal layer of the endopelvic fascia. This situation can result in either a localized pelvic abscess or in pelvic cellulitis. The latter condition is due to the continued breakdown of fat throughout the pelvis under the pressure of infection, which follows the path of least resistance. Because of the connection between the endopelvic and endoabdominal fascias, it is actually possible for infection to continue upward in the retroperitoneal fat to produce a perinephric abscess.

Infection of the perirectal space can occur even in the absence of penetration of the rectum when this space is not adequately decompressed surgically after a missile enters its confines. It was possible for us to study this type of lesion in a patient who had suffered multiple severe shell fragment wounds which penetrated the thighs, legs, feet, back, and buttocks, with several compound fractures, including that of one femur. This patient died 6 days after injury following the development of clostridial myositis (Clostridium oedematiens) of the thigh. The missile which penetrated the buttock passed through the

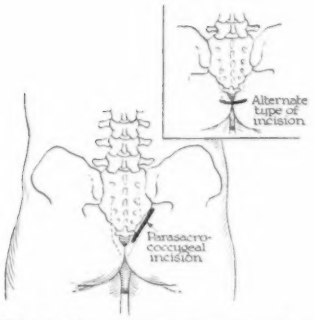


Fig. 4. Skin incision for parasacrococcygeal approach to incision of rectal portion of endopelvic fascia. Insert shows curved transverse incision below tip of coccyx as an alternate type of approach.

gluteal muscles and the sciatic notch, penetrating the rectal portion of the endopelvic fascia, but spared the rectal wall. A sigmoid colostomy had been done because of contusion of the rectal mucosa, but the foreign body lying next to the rectum could not be removed, nor could the perirectal space be decompressed because of the patient's desperate condition. The patient's postoperative condition never warranted a second operation to incise the perirectal fascia. This unfortunate situation afforded us, nevertheless, an opportunity to study the pathological consequences of contamination of the perirectal space from without, uncomplicated by fecal contamination from within the rectal lumen, as well as to observe the effects of inadequate decompression of the perirectal space. Postmortem examination of the tissue about the perirectal missile revealed a liquefaction necrosis of the perirectal fat extending for several centimeters around the missile, which was a jagged piece of metal with a small piece of cloth. The rectal mucosa was intact and the missile plugged the tear in the fascia, thus allowing no escape for the enclosed space infection. Though this lesion was not responsible for the patient's death, it could well have led to pelvic cellulitis or abscess formation. The routine administration of penicillin to this patient may have limited the spread of infection, but only adequate surgical decompression of the perirectal space and removal of the foreign body could have allowed healing to take place.

The initial operative treatment of penetrating wounds of the rectum is designed to prevent this series of events by employment of the following procedures: (a) complete débridement of the tract; (b) adequate incision of the rectal portion of the endopelvic fascia (so called "fascia propria") with suture of the rectal wall when the defect is large; (c) construction of a temporary, occlusive colostomy designed to divert completely the fecal current and to prevent recontamination of the wound from within. Some details of the technique employed in these procedures will be mentioned.

Removal of the coccyx does not, in itself, accomplish drainage of the perirectal space. Coccygectomy may or may not be a part of the operation, depending upon the individual case. Further, not only is coccygectomy unessential in most cases, but it may actually contribute to certain postoperative complications.

In the early cases of our series we were performing coccygectomy almost routinely as a preliminary step to incision of the rectal portion of the endopelvic fascia. Surgeons in the base sector hospitals noticed instances of osteomyelitis of the sacrum and pain in the region of the coccygectomy in a few patients evacuated to them for secondary care (3). As far as we can determine, neither of these complications occurred in any of our cases. However, we agreed that not only could adequate drainage of the proper spaces be obtained without coccygectomy, but that a longer incision could be made in the endopelvic fascia if the parasacrococcygeal incision was employed without coccygectomy (Fig. 4). Coccygectomy was reserved for those cases in which the foreign body actually fractured or partially destroyed the coccyx. When the sacrum was perforated, the bony defect was débrided and the parasacrococcygeal incision made without coccygectomy.

In doing the parasacrococcygeal drainage, it is important to recognize the various anatomical layers as they are incised. After traversing the skin and subcutaneous fat, the following layers can be recognized: superficial fascia; gluteus maximus muscle near its origin on the lateral aspects of the sacrum and coccyx; the thick, white fibers of the fused, heavy ligaments (consisting of the superficial posterior sacrococcygeal ligament, the sacrotuberous ligament and the short posterior sacroiliac ligament); loose areolar tissue; the relatively thin rectal portion of the endopelvic fascia.

With a finger in the rectum, the rectal portion of the endopelvic fascia is incised, thus exposing a thin fatty layer (perirectal fat). This fat may be blood stained and not easily recognizable, but with careful dissection, is unmistakable. In some instances the rectal finger may stretch the mural structures excessively, giving the surgeon the impression that the fascia must certainly have been

traversed because of the thinness of the tissues drawn over the finger. If the fatty layer is not identified, the proper fascia has not been incised, or the fatty layer has not been recognized. The incision in the rectal portion of the endopelvic fascia can be carried the entire length of the skin incision. Since the incision does not involve mural musculature of the rectum or anus, there is no reason to fear incision of the internal sphincter.

The incision described is done on the side of the penetration into the rectum. If there are two perforations it is done on the side having the larger defect. It need not be done on both sides. If the opening into the rectum is large and can be readily found, it is closed with either interrupted sutures or a continuous suture of silk, bringing mucosa to mucosa. If the defect cannot readily be seen, and proctoscopy has shown it to be small, it need not be sutured, since the contraction of the mural fibers in bowel at rest will permit the edges to meet and seal.

In the opinion of some surgeons, adequate drainage can be secured through a transverse, curved incision inferior to the tip of the coccyx, incision of the rectal portion of the endopelvic fascia and opening of the perirectal space by blunt dissection (Fig. 4). This technique was not employed in any of our cases.

When coccygectomy is indicated, it is important to do a complete excision. To leave the proximal segment of the coccyx or a portion thereof, usually results in pain on sitting as a late complication. Excision of the coccyx is done with a scalpel. As a rule, no bone cutting instrument need be employed. The coccyx is disarticulated at the sacrococcygeal joint and the remaining cartilage on the articular surface of the sacrum is removed with a curette. If cartilage is allowed to remain, it may become necrotic. Extensive partial sacrumectomy is probably an unnecessary procedure in most cases. If the wound has perforated the sacrum it is only necessary to remove contaminated and devitalized bone by curettement. If the posterior opening into the rectum is large and lies under the sacrum, it can be sutured through the parasacrococcygeal incision without destroying a large portion of the sacrum for this purpose.

There is no need to discuss in detail the débridement of the soft tissue wound. Suffice it to say that this should be thorough, with provision made for adequate drainage by generous incision of fascia.

The posterior portion of the operation (débridement and decompression) is best done before the colostomy is made, since it is preferable to complete the operation with the patient lying upon his back. It is well known that turning a patient toward the end of a time-consuming operation has a more profound effect on the patient's blood pressure than if he is turned early in the procedure. Furthermore, by doing the posterior portion of the operation first, it need not be rushed as it might be if done as a last minute procedure with the patient's blood pressure dropping. The only instance in which the abdominal portion of the operation is done first is in the case of active intra-abdominal hemorrhage.

The abdominal incision employed in cases requiring colostomy is usually a right paramedian incision. This incision allows somewhat more room for the occlusive dressings which separate the incision from the left iliac colostomy than would an incision on the left side of the midline.

It is not within the scope of this paper to describe the operative treatment of intra-abdominal penetrations, other than to state that a routine inspection of the intraperitoneal viscera is made, and all visceral perforations closed, including the perforation in the peritoneum caused by the missile, before the colostomy is made. It might be mentioned that perforations in the anterior, intraperitoneal wall of the rectum usually bleed profusely, and may be the only source of bleeding in a patient in severe shock due to intraperitoneal hemorrhage.

The usual site for the temporary colostomy in cases of rectal injury, is the sigmoid colon. However, if any portion of the transverse or descending colon has been perforated by a concomittant injury, exteriorization of this portion of the bowel can be employed as the site for temporary colostomy. When the right colon or cecum is perforated as well as the rectum, it is advisable to perform a sigmoid colostomy in addition to whatever procedure is carried out on the right colon.

In instances of severe destruction of the rectum which will require extensive reconstruction at some future time, it is best to perform the colostomy in the transverse colon with the two stomata completely separated by a bridge of skin. The surgeon doing the reconstructive surgery will then be able to mobilize sigmoid colon downward, if necessary, for the repair of the defect.

Our decision as to which type of sigmoid colostomy to perform—spur or loop—has been governed largely by the expressed preference of the surgeons in the base sector to whom our cases were evacuated. Some preferred to close the colostomies by crushing a long spur; others claimed it was easier to suture the loop colostomy

and return it to the abdomen. In a recent comparative study it was found that the percentage of successful closures was about the same in both types. The problem thus resolves itself to one of individual preference of the surgeon doing the closure. Regardless of which type is done, its main purpose is to divert the fecal current. It must place the rectum at rest by preventing any newly formed feces from being packed into the rectum. Stretching of the wall of the rectum can cause contamination of the perirectal tissues by the seepage of material through the wound in the wall.

The technique of colostomy will not be entered into in detail here, since the salient features have been emphasized repeatedly in the literature. The usual precautions of mobilizing sufficient colon to permit a generous portion of exteriorized bowel to protrude without tension, were followed in our series. The left iliac muscle-splitting incision was placed as far lateralward as possible. When indicated, the lateral peritoneal gutter was obliterated by tacking the colon to the peritoneum.

Most of our colostomies were opened immediately after operation and a Paul tube placed into the proximal loop. This was removed after 24 hours. All loop colostomies were treated in this manner. In some instances of spur colostomy, the bowel was clamped at the time of operation, and the proximal loop opened 24 hours after operation for the insertion of a catheter. In such cases the catheter was removed after an additional 24 hours, and the bowel was divided at the site of the clamp.

In no case was lavage of the distal loop carried out, on the premise that whatever fecal material remained in the distal loop soon became dehydrated and stationary, and might even serve as a "splint" around which the rectal wall could be immobilized, thus permitting healing to progress unimpeded. It is our impression that reinfection comes from new, moist fecal material and from activity of the rectal wall, rather than from inspissated, dehydrated contents.

Some mention should be made of the preoperative and postoperative care of these patients. All patients who were suspected of having an injury of the rectum were given the same operative priority as were patients with penetrating wounds of the abdomen; they were placed in the shock ward where they could get closer attention than in the preoperative wards during a large influx of patients. Here they were carefully examined, and a record was made of temperature, pulse, respiratory rate and blood pressure. Patients with penetrating wounds of the rectum were typed and their blood cross-matched for blood transfusion. If the patient was in good condition, this procedure was nevertheless carried out so that blood would be available and ready at the time of operation. Patients in shock received an emergency transfusion of 500 cubic centimeters of low titer type o blood from our blood bank together with 200 cubic centimeters of a 2 per cent solution of sodium bicarbonate intravenously, while their blood was being cross-matched for further transfusions. Most patients had received infusions of plasma at the battalion aid station or regimental aid station. Those in good condition were usually somewhat dehydrated on admission to our hospital. Such patients received an intravenous infusion of 1000 cubic centimeters of 5 per cent dextrose in normal physiological solution of sodium chloride, or in water, slowly. Roentgenograms were taken after the systolic blood pressure stabilized over 100 millimeters of mercury. A urine specimen was obtained from each patient, by catheterization if necessary, and an immediate urinalysis was done. Chemotherapy was instituted on admission of all patients. Early in our series, this consisted of administering 2.5 grams of sodium sulfadiazine dissolved in the intravenous solution preoperatively. Postoperatively, 5 grams of sodium sulfadiazine was given daily, in two divided doses 12 hours apart, dissolved in the intravenous solutions until the patient could take the drug by mouth. He was then given 1 gram of sulfadiazine with 4 grams of sodium bicarbonate every 4 hours. Daily urinalyses were checked for sulfadiazine crystals, *p*H, and microscopic hematuria. Records were kept of fluid intake and output. Since May, 1944, all patients received intramuscular injections of penicillin, 25,000 units every 3 hours, beginning on admission and continuing until the patients were well along in their postoperative course. A Levin tube was inserted into the stomach of patients suspected of having penetrating wounds of the abdomen.

Every patient operated on for a penetrating wound of the rectum received a blood transfusion during the operation, in amounts varying from 500 to 2000 cubic centimeters, depending on the requirements. Endotracheal gas-oxygen-ether anesthesia was used in all cases.

The postoperative management depended to a considerable extent upon the nature of the concommittant injuries. For example, those patients with penetrations of intraperitoneal viscera were treated with Wangensteen suction, intravenous therapy, and parenteral vitamins for approximately 4 days. Those patients whose only vis-

ceral wound was one of the rectum were allowed to have fluids by mouth beginning 24 hours after operation. Within 72 hours, their diet was usually converted to a "dry" diet to prevent a loose irritating stool at the colostomy.

The patients were kept at our hospital for a postoperative period ranging from 9 to 15 days, and were not evacuated to the base until they were in good condition.

ANALYSIS OF CASES

The interval between the time of wounding and the time of operation averaged 21 hours in our series, the extremes being 8 hours for the shortest time interval and 55 hours for the longest. Most of the long interval cases resulted from delay in evacuation in the mountainous terrain of the Cassino campaign, in the winter of 1943–44. During this campaign most of the wounded had to undergo a dangerous, time-consuming trip, being first carried by shuttles of litter-bearers down icy, treacherous mountain trails, often followed by a further trip by mule pack, and finally a long ride in an ambulance which had to pick its way along rough, partially destroyed mountain roads. Although the terrain was even worse in the winter campaign of 1944–45, the casualties reached us in a shorter time because of ingenious improvements in methods of evacuation from the mountains, such as ski-litters and cable baskets. Once the patients reached our evacuation hospital, the average time between admission and operation was 4½ hours for our series of rectal injuries. Generally, 2 hours was the minimal time necessary for resuscitation, examination, roentgenography, and preoperative preparation.

The location of the wounds of entrance in our cases is worth noting. In 4 cases the wound of entrance was in the thigh. One of these had caused a compound fracture of the femur. In 3 cases the wound was in the hip area, and in one case it was above the iliac crest. These data lend importance to the warning that the rectum may be perforated in instances in which the wound of entrance is remote. In 9 cases the missile caused a compound fracture of the sacrum, coccyx, or pelvic bones. Six of these entered through the sacrum. Eighteen wounds of the rectum were the result of wounds of the buttocks (Fig. 5).

In 21 instances, multiple wounds were present. Of these, 7 had penetrated intraperitoneal viscera, while in 2 patients the urinary bladder was perforated. Ten patients had concomitant wounds of extremities. Of these, 2 involved major vessels, 1 the sciatic nerve, and there were 5 compound fractures of the extremities. Two patients had

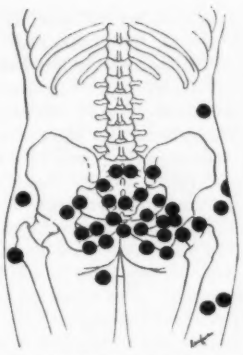


Fig. 5. Diagram showing location of wounds of entry of missiles which penetrated or perforated the rectum in series of 35 consecutive cases. This emphasizes the fact that wounds of entry may be remote.

thoracoabdominal wounds. It is these cases of multiple injuries which tax the endurance of the surgeon and which require painstaking clinical evaluation before surgery as well as diligent after-care.

Postoperative complications occurred in 5 cases. In 2 instances, secondary hemorrhage from the middle sacral artery occurred, one 6 days after operation and one 8 days after operation. Both of these patients had had coccygectomies. The hemorrhage was arrested in both cases, and blood volume was restored. Both had uneventful courses thereafter up to the time of evacuation 15 and 14 days postoperatively, respectively.

In the other 3 cases, the complications led to death of the patient, although in only 1 case did the complications result from the rectal wound. These 3 cases constitute the total mortality in our series of rectal wounds, and represent 8.5 per cent of the series. In 1 case, abstracted previously in this paper, the rectum was contused, but not penetrated, although the missile entered the perirectal space. As stated, this patient died as a result of clostridial myositis of the thigh muscles following severe penetrating wounds of this part and a compound fracture of the femur.

In the second case death was due to extensive damage to the parenchyma of both lungs and severe shock. The patient suffered multiple wounds of the back, one of which perforated the sacrum and penetrated the rectum. In the right chest there were comminuted fractures of the 7th and 8th ribs with laceration of the pleura, penetration of the right lower lobe with extensive interstitial hemorrhage and hemothorax. The missile which entered the left chest caused com-

minuted fractures of the 10th and 11th ribs, laceration of the pleura, hemopneumothorax, severe interstitial hemorrhage of the left lower lobe, perforation of the diaphragm and laceration of the spleen. Besides these wounds, there were multiple penetrating wounds of the legs, arms, neck, and scalp, and a compound comminuted fracture of one foot. The right kidney was contused and there were cortical hemorrhages in both suprarenal glands. The patient was admitted 6 hours after injury, in profound shock. Desperate efforts were made to treat the shock, but response was poor. Operation was undertaken on the basis of continued intra-abdominal hemorrhage. Through a laparotomy incision a splenectomy was done and a large tear in the left diaphragm was sutured. A sigmoid colostomy was brought out through a left iliac muscle-splitting incision. The penetrating wounds of the chest were débrided and the deep layer was closed. Thoracenteses were done, and all wounds were débrided. The perirectal space was drained. Although the patient rallied immediately after operation, he never did fully recover from the state of shock, and died on the first postoperative day. In this case the rectal injury was of secondary importance and can hardly be implicated as a cause of death.

The third case illustrates the spread of infection along the anatomical planes described earlier in this paper. The patient reached our hospital 38 hours after injury during the Cassino campaign. He was in severe shock, but responded to the usual treatment of massive blood transfusions and supportive measures. He had multiple wounds of the buttock, thigh, and leg, with evidence of a gas-producing clostridial infection of the thigh wound. There were two perforations of the extraperitoneal portion of the rectum, the patient's abdomen was rigid, and there were diminished peristaltic sounds. At laparotomy, no visceral perforations were seen, but about 2 ounces of turbid fluid was found in the lower peritoneal cavity. A small area of necrosis was noted on the anterolateral portion of the rectum at the peritoneal reflection. Gas was discernible in the retroperitoneal region over the left iliopsoas muscle. Definite crepitus was noted with digital pressure on the posterior peritoneum in this region. A sigmoid colostomy was made. Coccygectomy with drainage of the perirectal space was done and the wounds of the extremities were débrided radically. There was no major vascular damage in the thigh, but the muscle damage was extensive and showed signs of clostridial myositis. Despite all efforts, including antitoxins, penicillin and blood transfusions, the patient developed a severe toxemia and died 4 days after operation.

At postmortem the diagnosis of a clostridial gas-producing infection of the thigh was confirmed. Regarding the rectal lesion and the gas in the retroperitoneal space, the following excerpt from the autopsy protocol[1] is of interest.

> On the anterolateral aspect of the lowermost portion of the intraperitoneal rectum at the peritoneal reflection is an irregular, patchy gray area of necrosis measuring 7 by 4 centimeters. This is on the right side. Dissection of the perirectal tissues reveals two tracts passing from the left obturator canal into the substance of the rectal wall where they perforate the mucosa of the rectum 6 centimeters apart, the highest at the level of the peritoneal reflection. These perforations are on the posterolateral aspect of the rectum on the right. The margins of the mucosal openings are ragged and gray, and no foreign body can be located in the rectum or rectal wall. The pararectal tissues along the tracts and the perirectal fat at a distance from them exhibit a grayish green gelatinous edema and necrosis with no localization of purulent material. This edema extends to the brim of the pelvis posteriorly, but there is no evidence of gas-producing infection here. It is likely in view of the findings in the perirectal tissues that the gas encountered in this region was derived from the lacerations in the rectal wall, and not from the infection in the thigh, since there is no direct connection between the two areas of infection.

In this case the spread of infection under the endopelvic fascia had already taken place before the patient came to surgery. Whether the posterior decompression and colostomy, ordinarily preventive measures, might have been successful as therapeutic measures in the presence of an already established infection, had the gas infection of the thigh not caused the patient's death, remains an unanswered question. This case illustrates the consequences of a long time lag before surgery in certain instances. However, there were several other cases in our series with even longer time lags in which recovery followed initial surgery. This was the only instance in the series in which a spreading pelvic infection was seen.

FOLLOW-UP

Since patients with rectal injuries did not leave our hospital until they were in good condition, there was little reason to expect infection to occur at a subsequent date. However, questionnaires were sent out to base sector hospitals asking for follow-up information on those patients which the author could not visit at the base. Information was obtained in 21 of our 35 cases, giving us a representative cross section of the disposition of the cases.

The follow-up covered an average period of 67 days after the patients left our hospital. Contact

[1] Postmortem examinations were performed by Major Leo Kaplar, M.C., A.U.S.

was lost once the patients were sent to the zone of interior, but all such patients were sent out in "good condition." Of 21 patients on whom follow-up was possible, there were no deaths. Colostomies were closed in the overseas theater in 13 instances. Of these patients, 2 were returned to limited overseas duty, while 11 were sent to the zone of interior. Some patients who might otherwise have had closure of colostomies overseas, were sent to the States without closure because of the severity of concomitant injuries or for reasons of general expediency. It is difficult, therefore, to estimate what percentage of patients with injuries of the rectum can be expected to return to limited overseas duty. Since there were no complications in any of the cases in which follow-up was possible and since those who were sent to the States left the overseas base sector in good condition, we can also feel justified in expecting a satisfactory recovery, as far as the rectal injury is concerned, in most patients whose colostomies were not closed overseas.

DISCUSSION

The notable absence of complications due to infection in the follow-up period of our series, and the almost complete absence of pelvic cellulitis (except in one case, in which this was present before surgery), bring up several questions pertinent to the initial surgical management in cases of rectal wounds. How many of these patients would have developed complications if the surgery had been less radical? Was colostomy necessary in every case? What about those cases in which posterior decompression was obviously inadequate, and which nevertheless had an uneventful course? What rôle did chemotherapy play in the outcome of these cases? What was the course of those patients in whom a rectal injury was not discovered?

Certainly the answers to these questions cannot be found in an analysis of our limited series. Perhaps, at some future date, after reports are compiled from theaters of operation throughout the world, it will become possible to state criteria on which to base the selection of cases of rectal injury for radical initial surgery. However, some parts of these questions can be clarified from our experience.

We have felt safer in attempting to decompress the perirectal space and in diverting the fecal stream at the initial operation since it was necessary to evacuate the patients to rearward areas after approximately 10 days. The patients passed through the hands of several surgeons at various institutions, and it was impossible for the original surgeon to follow each case to its conclusion. It was, therefore, in all probability, a safer procedure to design the initial surgery to prevent exigencies which might otherwise arise. In civilian practice, many of our patients might have been carried along under close observation until it could be definitely determined whether or not a colostomy should be performed.

Those patients in whom posterior decompression was obviously inadequate, but who nevertheless had uneventful courses, probably had drainage through the opening caused by the missile. Surgeons at the base sector hospitals have observed an occasional case of pelvic abscess developing late, but this complication was rare, and as far as we can determine, did not occur in any of our cases.

The exact rôle of chemotherapy in cases of rectal injury is unknown. There has been no noticeable difference in the course of our patients treated with sulfonamides and those treated with penicillin, despite the fact that penicillin has no effect on bacteria of the colon group. It is our impression that the initial surgery was the main feature in the treatment, with chemotherapy serving as an adjunctive control of infection.

As to the course of patients in whom treatment was delayed or in which a rectal injury went undiscovered, we have two opposite types of cases to cite. One had an extremely rapid spread of pelvic infection within 38 hours, while the second developed no ill effects whatever, up to 8 days following rectal injury. The first case, already abstracted, was one in which the patient developed an extensive pelvic and retroperitoneal infection within 38 hours after injury, before surgery was undertaken. As stated, this patient died from a toxemia and clostridial infection of a thigh wound, so that clear cut evidence of the effects of the pelvic infection could not be appraised. It is known, however, that this type of case carries a high mortality rate. In the last war, for example, pelvic cellulitis from rectal wounds resulted in a fatal issue in 45 per cent of cases (4). For purposes of illustration, this case represents the rapid spread of pelvic infection from a rectal wound despite the use of prophylactic penicillin therapy.

By contrast, is the case of a patient with a perforation of the rectum who reached our hospital 6 days following injury without surgical treatment. He was a German soldier who was admitted from a German *Feld Lazarett* during the overwhelming influx of prisoner-patients shortly after the mass surrender of the enemy in northern Italy. His wound was a transversely perforating gunshot wound entering the left trochanteric area and

emerging in a similar area on the opposite side. The only treatment he had received in the 6 days since wounding was an occasional dose of a German sulfonamide. The patient stated that he had had a few bloody stools for one or two days following injury, but bowel movements had been normal since then. There were no fractures or signs of vascular injury. Proctoscopic examination revealed a laceration about 1 centimeter long in the posterior portion of the rectal mucosa 5 centimeters from the anus. The wound contained a bit of clotted blood and the surrounding mucosa appeared normal. There was no evidence of perirectal abscess. The external wounds were clean and dry. Temperature, pulse, and respirations were normal. In view of the patient's excellent condition and the 6 day interval since wounding, it was decided that a conservative policy be followed. Hence no surgery was done by us and the patient was placed on penicillin therapy and watched. He was followed for a period of 2 days at our hospital during which time he had no elevation in temperature, nor was he particularly uncomfortable. He was evacuated as a litter patient in good condition to a rearward installation.

This case illustrates the fact that there are some cases of rectal injury in which major surgery is not necessary for the recovery of the patient. But what criteria can the surgeon rely upon to determine in which cases of rectal injury major surgery will be required and in which ones it will not? Plainly, there are no such criteria available at the present time. This fact has been largely responsible for our policy of performing a colostomy and decompressing the perirectal space in all cases of wartime injuries of the rectum. The results of this surgical policy have been most encouraging, and have brought about a remarkable reduction in both mortality and morbidity as compared with previous statistics. Until new criteria can be established for proper selection of cases for nonintervention, we believe that we should rely upon these surgical measures as insurance factors in all wartime injuries of the rectum.

SUMMARY

Experiences and results in the initial surgical management of 35 consecutive cases of battle injuries of the extraperitoneal portion of the rectum are reviewed. Important aspects of the diagnosis of such cases are presented. Rectal injuries in wartime are usually associated with multiple injuries of other structures, and it is important that the rectal injury not be minimized or overshadowed by the presence of other, apparently more serious, wounds at the time of initial examination. The anatomical relationships of the endopelvic fascia are reviewed to emphasize the purposes and aims which initial surgery must accomplish in order to prevent pelvic infection. The two main features of the initial surgery are: (1) decompression of the perirectal space by adequate incision of the rectal portion of the endopelvic fascia (so-called "fascia propria") and (2) colostomy, to divert the fecal current until the wound is healed. The surgical technique is described. During a follow-up period averaging 67 days in 21 cases, there was a remarkable absence of complications from infection. Certain questions pertaining to the care of rectal injuries remain unanswered, such as the rôle of chemotherapy and the selection of cases for nonintervention. The policy which we have followed and which is, in our opinion, the safest under conditions of warfare consists of surgical intervention as described herein, supplemented by chemotherapy, in all cases of penetrating wounds of the rectum.

REFERENCES

1. Gordon-Watson, Charles. Surgery of Modern Warfare by Hamilton Bailey. Vol. 1, 2d ed., 426–432. Baltimore: Williams & Wilkins Co., 1942.
2. Gray's Anatomy. Edited by Warren H. Lewis, p. 418, 24th ed. Philadelphia: Lea & Febiger, 1942.
3. Hurt, Lawrence E. Med. Bull. Mediterranean Theater Operations, 1945, 3: 34–37.
4. Military Surgical Manuals, National Research Council. Abdominal and Genitourinary Injuries. Philadelphia: W. B. Saunders Co., 1942.

THE USE OF CURARE IN ANESTHESIA FOR THORACIC SURGERY

Preliminary Report

PHYLLIS HARROUN, M.D., and HUBERT R. HATHAWAY, M.D., San Francisco, California

MOST thoracic surgeons in this area agree that the optimum operating conditions for intrathoracic disease, and also the least physiological upset to the patient, are afforded by the so-called "apneic technique" of anesthesia, the patient's lungs being intermittently inflated by gentle pressure on the breathing bag. However, this procedure necessitates the use of potent anesthetic agents, all of which with the single exception of chloroform, are explosive, thus contraindicating the use of the cautery once the pleura is opened. Most anesthetists consider chloroform too toxic a drug to use over the long periods required for intrathoracic surgery.

Although spinal analgesia permits the use of the cautery inside the chest in cases of thoracic surgery, few anesthesiologists have availed themselves of this method as a means of producing apnea. Therefore, in our opinion, "controlled respiration" cannot be used satisfactorily in these cases.

When curare was first utilized as a relaxing agent in anesthesia for abdominal surgery it was claimed that its danger lay in its faculty of producing respiratory depression, which might even proceed to apnea if unduly large doses were used. As a result of this statement, we conceived the idea of using this property of curare for the production of apnea during intrathoracic operations. If this proved practical, nonexplosive nitrous oxide could be utilized as the anesthetic agent and the surgeon could use the cautery inside the chest.

To date this technique has been used on 11 patients undergoing intrathoracic operations in this hospital. The cautery has been used within the pleura in every case. It has proved easy to produce apnea and control breathing, and no difficulty has been encountered in any case in persuading the patient to resume spontaneous respiration. The use of prostigmin for this purpose has not been found necessary. The patient's general condition during the operation and postoperative course has been excellent in all cases. The only complications which could be even remotely attributed to curare are 3 instances of postoperative atelectasis. These may be attributed to the type of operation and the result of the medication.

From the Subdivision of Anesthesia, Department of Surgery, University of California Medical School, San Francisco.

TECHNIQUE

On the morning of operation, the patient is heavily medicated with a short acting barbiturate, morphine and scopolamine, so that he will be brought to the operating room just sufficiently awake to move from bed to table. A nitrous oxide and oxygen mixture is administered by means of a face mask. If any difficulty is encountered in producing anesthesia smoothly, enough sodium pentothal is injected intravenously to attain satisfactory anesthesia. (Pentothal is rarely necessary.) During induction particular notice is taken of the proportion of nitrous oxide and oxygen necessary to keep the patient in first plane anesthesia and well oxygenated. A pharyngeal airway is inserted and the anesthetist's ability to inflate the lungs by pressure on the breathing bag is tested. We consider it unwise to administer curare unless a perfectly free airway allowing inflation of the lungs exists. A quantity of curare[1] calculated to be sufficient to stop spontaneous respiration is then injected intravenously. No particular precautions about speed of injection are taken. This first administration usually amounts to 150 to 200 milligrams of curare. Complete apnea or at least profound respiratory depression usually follows in from 30 seconds to 2 minutes. The patient's lungs are then inflated by gentle intermittent pressure on the breathing bag. After approximately 5 minutes, when the maximum relaxation has been attained, the mask is removed and an orotracheal tube with an inflatable cuff is inserted under direct vision. The profound muscular relaxation usually makes intubation an easy matter. This tube is connected to a canister of soda lime and a breathing bag, the delivery tube from the anesthesia apparatus is attached, and anesthesia is continued, the same concentration of nitrous oxide and oxygen being used which was previously found to keep the

[1] Intocostrin (Squibb).

THE USE OF CURARE IN ANESTHESIA FOR THORACIC SURGERY: REPORT OF 11 CASES

Case number	Age	Preoperative diagnosis	Operation	Duration of anesthesia	Duration of apnea	Total dose of curare	Postoperative complications	Day of discharge postoperative
I	60	Malignant tumor L.L.L.	Lobectomy L.L.L.	3 hrs. 40 min.	2 hrs.	300 mgs.	Pleural effusion 2nd week	22
II	57	Carcinoma of stomach	Transthoracic gastrectomy	6 hrs. 50 min.	4 hrs. 35 min.	400 mgs.	Headache, 4 days	16
III	40	Bronchogenic carcinoma	Pneumonectomy left	4 hrs.	2 hrs. 15 min.	320 mgs.	Died 3 days postoperative of cerebral metastases, proven at autopsy	3
IV	48	Carcinoma of esophagus	Exploratory thoracotomy	3 hrs. 45 min.	2 hrs. 5 min.	260 mgs.	None	10
V	53	Bronchogenic carcinoma L.U.L.	Exploratory thoracotomy	3 hrs. 30 min.	2 hrs. 45 min.	330 mgs.	Pleural effusion duration 7 days Fever, duration 4 weeks	43 (Kept in for x-ray therapy)
VI	19	Intra-abdominal abscess	Drainage of splenic abscess opening into pleura, splenectomy	3 hrs. 25 min.	1 hr. 5 min.	400 mgs.	Tachycardia, duration 3 days Headache, 1 day	18
VII	30	Bronchocutaneous fistula with abscess formation	Eloesser flap drainage of lung abscess	1 hr. 45 min.	55 min.	200 mgs.	Fever, 6 days	16
VIII	38	Diaphragmatic hernia	Repair of diaphragmatic hernia	3 hrs.	1 hr. 45 min.	300 mgs.	Atelectasis, 1 day	11
IX	20	Bronchiectasis L.L.L.	Lobectomy L.L.L.	4 hrs. 15 min.	2 hrs.	370 mgs.	Atelectasis, 3 days	19
X	61	Carcinoma of esophagus	Esophagectomy	6 hrs. 50 min.	6 hrs. 40 min.	360 mgs.	Atelectasis, 1 day	15
XI	50	Bronchogenic carcinoma R.L.L.	Pneumonectomy	5 hrs. 25 min.	3 hrs. 30 min.	380 mgs.	None	Still in hospital

patient well anesthetized and well oxygenated. This is an important point, since once the muscular paralysis of curare has set in, the signs of anesthesia, all of which are muscular, are completely masked. The patient is placed in the desired position, prepared and draped in the usual manner. A continuous drip of normal saline is started in an arm or hand vein with a 3 way stopcock with a syringe of curare on the side-arm so placed that it will be conveniently within reach of the anesthetist. The operation is then started.

Spontaneous respiration is usually resumed in 20 to 30 minutes after the initial dose of curare. As soon as the respirations are sufficiently deep to provide adequate inflation of the lungs, the patient is allowed to breathe spontaneously until just before the pleura is opened. Another dose of curare sufficient to stop respiration is then administered. It will usually be found that 60 to 100 milligrams will produce apnea at this time. When respiratory depression appears, intermittent gentle pressure of the breathing bag is resumed, since excess of carbon dioxide or lack of oxygen may cause attempts at spontaneous respiration after a dose of curare which would otherwise be adequate to produce apnea. If the patient is still breathing 5 minutes after the first dose, a second dose is administered; further doses are given at 5 minute intervals until apnea is attained. Whenever respiration is resumed by the patient, 20 to 40 milligrams of curare (or more if necessary) are given, thus maintaining the desired respiratory arrest as long as the pleura is open.

If, as frequently occurs during long operations, the preoperative medication wears off, it will be found that the anesthetic mixture which had previously kept the patient anesthetized is no longer adequate. This will not be evidenced by the usual signs of light anesthesia since, as was previously explained, the signs are masked. Diaphragmatic contractions, slight muscular twitchings, movements of the facial muscles, or a rise in blood pressure may occur instead. These phenomena are indications for the administration of a further dose of morphine.

The patient is kept in apnea by means of small repeated doses of curare as long as the pleural cavity is open. As soon as an airtight closure has been effected by the surgeons, pressure on the breathing bag is stopped and the patient is allowed to build up carbon dioxide in his blood stream. Spontaneous respiration will usually be resumed in about 1 minute. If it is not resumed by the time slight cyanosis occurs, controlled respiration

is continued. A similar attempt is made every few minutes until the patient breathes spontaneously. This will almost always occur within 5 minutes unless an unnecessarily large quantity of curare has been given just before the pleura was closed. The patient is then allowed to breathe for himself, but until the intercostal muscles are functioning adequately, an occasional squeeze of the breathing bag will keep the upper lobes from becoming atelectatic.

The patients are usually awake and able to answer questions before leaving the operating table, even after operations lasting 6 hours or more. However, it must be remembered that the residual muscular weakness, which persists for several hours, makes careful after-treatment necessary. The patient should be placed in bed on his side and turned frequently from one side to the other. Coughing should be encouraged. Oropharyngeal oxygen should be given if indicated by the presence of dyspnea, rapid pulse, or cyanosis.

The surgeons at the University of California Hospital are enthusiastic about this type of anesthesia, combining as it does the advantages of controlled respiration with the convenience of the cautery. The excellent condition of the patients during the operation and their good postoperative course have been very gratifying. However, this method is still on trial; a much larger series of cases will be necessary before final judgment can be passed on the safety of curare for intrathoracic surgery.

EDITORIALS

SURGERY
Gynecology and Obstetrics

FRANKLIN H. MARTIN
Founder and Managing Editor
1905–1935

LOYAL DAVIS, Editor in Chief

Associate Editors
SUMNER L. KOCH MICHAEL L. MASON

M. E. SPENCER, Assistant Editor

DONALD C. BALFOUR, Associate, Editorial Staff

FEBRUARY, 1946

REORGANIZATION OF THE SURGICAL PUBLISHING COMPANY OF CHICAGO

IN accordance with the terms of the will of Dr. Franklin H. Martin, all shares of stock of The Surgical Publishing Company of Chicago at his death became the property of the American College of Surgeons subject to a life interest in the company in favor of Mrs. Isabelle Hollister Martin, his widow. Following her death, the management of The Surgical Publishing Company of Chicago, which publishes SURGERY, GYNECOLOGY AND OBSTETRICS, thus has become the responsibility solely of the American College of Surgeons.

The Board of Regents of the American College of Surgeons has elected a Board of Directors for The Surgical Publishing Company, an Executive Committee of the Board of Directors, and an Editorial Policy Committee.

The Board of Directors for the Surgical Publishing Company consists of the following:

Dr. Irvin Abell, *Chairman*
Dr. Arthur W. Allen
Dr. Donald C. Balfour
Dr Frederick A. Coller
Dr. Harry S. Gradle
Dr. Howard C. Naffziger
Dr. Dallas B. Phemister

The Executive Committee of the Board of Directors consists of the following:

Dr. Dallas B. Phemister, *Chairman*
Dr. Frederick A. Coller
Dr. Howard C. Naffziger

The Editorial Policy Committee consists of the following:

Dr. Donald C. Balfour, *Chairman*
Dr. Arthur W. Allen
Dr. Frederick A. Coller
Dr. Loyal Davis, *Ex-Officio*

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

SUDDEN death during convalescence has always been a most disturbing episode. Lay people have learned to dread it and doctors have long been depressed by this insidious and unexpected interference with the recovery of their patient. Massive pulmonary embolism from the leg veins is the most common source of this catastrophe. In the middle twenties, reports from large clinics showed that three persons in each 1000 subjected to surgery would die during convalescence from this cause. Much was done to prevent these deaths and by careful attention to frequent change in posture and efforts directed to diminish stasis in the leg veins, the ratio of fatalities from embolism was reduced to approximately 1 in 800. All this did not take into account the prolonged convalescence brought about by thrombophlebitis with the post-

phlebitic edema and subsequent leg ulcers so frequently seen in those who recovered.

Various studies directed toward this problem by many minds finally have brought about certain facts that are important. The development of bland thrombi in the leg veins that come about with no warning has been a new line of thought in recent years. Homans, of Boston, and Ochsner, of New Orleans, have contributed much to this subject. The former has preferred the term "bland thrombosis" and the latter that of "phlebothrombosis." These men have emphasized the importance of thrombosis that is noninflammatory and due to the lack of reaction in and about the vein, there is far greater chance of such a thrombus leaving the vein and being deposited in the lung. If small, this detached thrombus produces an infarct or, if massive enough, it may completely occlude the pulmonary artery producing death within a few minutes. This is a different type of thrombosis than occurs in thrombophlebitis. In this latter disturbance of the venous return, there is an inflammatory reaction that produces the painful, swollen extremity known as phlegmasia alba dolens. That infarct or fatal embolism is less common in this type of thrombosis is an established fact. This is doubtless due to the firm attachment of the clot to the wall of the vein present in this type of inflammatory thrombosis. We have found that phlebothrombosis will, often and in a higher proportion of cases in certain climates, become thrombophlebitis.

Efforts to prevent serious sequela from thrombosis of the leg veins have led us to seek methods to prevent the thrombosis in the first place and if thrombosis occurs to prevent death from massive embolism, and now to diminish the convalescence of such a victim even though a fatal embolus might be unlikely.

Anticoagulant drugs administered first after the thrombosis had become established came into vogue with the discovery and use of heparin. This method gave excellent results in many cases but due to the difficulties arising out of its use, it is now more generally relied upon as the adjunct to other forms of treatment. This drug could hardly be used routinely as a preventative unless the newer intramuscular type of heparin-in-oil proves to be innocuous, inexpensive, and reliable. Dicumarol seems to be satisfactory in the hands of experts as a preventative of serious thrombosis and has the advantage of oral administration and a low cost. However, it carries the absolute necessity for accurate laboratory control of the prothrombin level and, if great care is not exerted, the complications may outweigh its benefits. Serious hemorrhage that has proved fatal in some instances has occurred following its use. In all probability, further study and research along the lines suggested by the effects of heparin and dicumarol will eventually bring about a safe and satisfactory use of these or similar acting drugs.

Over ten years ago, Homans reported four instances of femoral vein interruption in patients who were having repeated infarcts from bland thrombosis. Due to the immensity of the problem in the Massachusetts General Hospital, there has come about a gradual but steady trend toward femoral vein interruption as an answer to this question. To August 1, 1945, 861 patients in this institution have been subjected to femoral vein interruption. At first, attempts were made to determine whether or not a thrombus existed, by phlebography—now this method has been abandoned. Early, we learned that the apparent sick leg might be misleading and that often the most dangerous thrombosis was lying dormant in the opposite, apparently normal, side. Therefore, we have gradually become convinced that bilateral interruption should be done. Much time, thought, and discussion

have entered into the subject regarding the site of interruption. Vena cava ligations have been carried out successfully by Linton in 14 instances. He is disturbed that two of these patients have developed postphlebitic edema with ulcer. Iliac interruptions have been sponsored by Homans, who felt that this more serious undertaking was justifiable in order to get above the clot and because the collateral circulation was better at that level than it was after femoral vein interruption. Common femoral vein interruption has been done in a considerable number of our cases, but we realize that the technical hazard is greater and that actually a serious acute edema can follow this procedure under certain circumstances. The majority of our patients have been subjected to interruption of the femoral vein distal to the profunda femoris. This permits an easy exposure of a segment of vein without branches to allow opening of the vein and the removal of thrombi proximally and distally by suction, and final complete division of the vein.

In this series, there has been no fatality as a result of the procedure. There have been surprisingly few instances of infection or lymphorrhea. Only one of the patients has developed a postphlebitic ulcer. The average hospital stay after femoral vein interruption has been about six days. Patients operated upon before leg swelling develops have no postoperative edema worthy of note. If the operation is undertaken after bland thrombosis has become inflammatory with pain and swelling, then a period of postoperative edema occurs. This edema may last several months depending on the duration of the thrombophlebitis before and after vein interruption. Approximately 6 per cent of the patients having had infarcts before operation will continue to have infarcts afterward. These may be serious enough to warrant the use of anticoagulant drugs. In one instance only was there a fatal embolism arising from the profunda femoris after superficial femoral vein interruption—this in a seventy-four year old man with widespread carcinoma arising from the stomach. He had evidence of thromboembolic disease on admission with immediate femoral vein interruption. His death occurred 8 days later.

This operation is so safe and so simple and if done on the normal vein produces so little swelling of the extremity, that prophylactic vein interruptions are being done with greater frequency. Up to the date of this writing, this procedure has been carried out in approximately 100 patients in our clinic. All of this group have been elderly patients, who for reason of their acute disorders, would need a prolonged period of bed rest. Typical of these are the aged with fractures of the hip region.

Control experiments are being carried out on a group of patients between the ages of 40 and 65 with dicumarol after operation. The results of this study may show that fewer femoral vein interruptions may be necessary in certain types of patients. We feel at this time that older individuals may be more safely managed by prophylactic femoral vein occlusion. Fatal embolism is so much less likely under the age of forty that signs and symptoms can be relied upon to determine the need of thrombectomy and venous interruption in younger patients. ARTHUR W. ALLEN.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

PERHAPS the most significant book that has emerged from the medical aspects of this war is Grinker and Spiegel's *Men Under Stress*.[1] Not only is it an important book, but also an interesting one, for it deals with a vital subject associated with war in an interesting, personal way. The two authors have put themselves into this book with enthusiastic competence. This gives to its many pages the elements of unusual industry, personal knowledge, experiences gained from combat observation and from close contact with every feature of the aviator's job and the weapons he is trained to use. There is technical information about these things which is unusual in most medical contributions which have come out of this war.

The case reports are fine examples of clinical reporting. They are generally brief and to the point, centering about and presenting the clinical symptoms while illustrating the significant situations producing the psychiatric picture. They contain relevant material for explanation, interpretation, and therapy. There are 65 of these case histories, which is perhaps too many and make the authors seemingly overeager to furnish proof of their ideas. The evidence is overweighted by this accumulation of data. This encourages repetition so that the book spins itself out to too great length.

Through the protocols of the soldiers, with their neuroses and the discussions which follow, the core of the authors' theory of the neuroses, which is built around anxiety and the struggles of the ego and superego, is nailed down.

The average reader will be so impressed with the mass of case material and the theories derived from them that he will have little doubt of their absolute validity. The critical reader, on the other hand, may be doubtful of the validity of any absolute statements about the human personality, especially when these statements concern the dislocation of the personality in the neuroses as substitutions of its pre-existing form.

In attempting to evaluate medical contributions which are written about this war, it is well to keep in mind the essential and necessary weakness of all war books written during it. This is especially true of those dealing with the medical aspects of war; for the atmosphere of war is not conducive to that critical restraint which is essential during peace time writing on the same subject. A study of the very large number of papers on the war neuroses published during and after the first World War will show the necessity for a critical examination of this book. The conclusions of its authors should not be regarded as final and absolute, despite their evident wish to have them so regarded.

There is little evidence of the necessarily tentative nature of our present day thinking on the subject covered by this book. A too ready acceptance of the meaning and interpretation of the war neuroses is not an advantage at the present time; but, it seems inevitable if this book is taken as the final answer. Neither the sincerity nor the competence of the authors can be questioned. Their therapeutic planning, the execution of the plans, and their successful management of individual cases, are also not questioned. The total conception of the war neuroses, as brought out in this book, however, cannot be accepted without a weighing of evidence and the critical analysis of the key implications of the personality structure of the aviator with war neurosis. If the authors' theses are accepted as fact, what is true for him, is true for every man, whether his neurosis be of war or civilian origin.

The authors' approach to the war neuroses is what may be called disguised Freudian. The psychoanalytic formulae are everywhere apparent, but seldom mentioned as such. This fact is disarming. The reader will find, much to his surprise, that he has been reading about the war neuroses from the point of view of psychoanalysis. The adaptations of the Freudian concepts of personality structure, anxiety, regression, identification, childhood experiences, the pain-pleasure principle, infantile trauma and so forth, to the neuroses of war are slipped in without any warning to the reader. He will be disarmed further by the omission, in great part, of the sexual implications in most of these and other concepts which are so deftly used to build up a body of Freudian doctrine which is nowhere acknowledged as such. Freud is not mentioned in the body of the book, nor in its preface. It is as though the authors planned it that way so as not to arouse opposition or prejudice against the theories that bear the burden of psychoanalytic thought. As understandable as this is, in the broad scheme underlying this book, the insinuation of the Freudian view and the use of Freudian hypotheses demand critical scrutiny, because, apart from the descriptions and clinical reports, this book gives a broadly conceived and convenient demonstration of the concepts of the Freudian psychology as the definitive and final interpretation of the war neuroses.

Prime importance is given to anxiety, both as an affective state in itself and as an affective state with

[1] MEN UNDER STRESS. By Roy R. Grinker, Lt. Col., M.C., and John P. Spiegel, Major, M.C. Philadelphia: The Blakiston Co., 1945.

demonstrable objective symptoms, as well as various combinations of both. From all these conditions, mental and emotional turmoil result. The articulate, descriptive ability is more evident in those instances in which objective symptomatic displays are less impressive. The authors use case histories to interpret and elucidate; first, the eternal struggle between the ego and the superego; second, the regressive drives as necessary accompaniment of the neuroses; and third, the enmeshing, constantly present anxiety. Anxiety works effectively, chiefly through the autonomic system, plus the important rôle played by the endocrine structures as an adjunct source of symptoms.

It may well be, that at the present time, there is no more adequate scheme of understanding the neuroses than the one used by the authors. It may well be that they believe their use of Freudian hypotheses, as applied to such an array of cases, is convincing proof of their validity. By continued use and repetition, the authors' theories assume the aspect of truth rather than remain a series of psychological hypotheses and speculations. Thus, these, in the conceptions of the authors, become absolutes. There is scarcely a page in which the ego and the superego, regression and anxiety are not mentioned. These concepts or working hypotheses become, in the reader's mind, established facts. They stand out, therefore, as sharply fixed as those facts which are experimentally derived in physics or chemistry or any science which depends, for validity, upon controlled experiments. But, despite repetition, these concepts remain working hypotheses and are, by no means, facts. That this is not overemphasized may be illustrated by mentioning the many terms used to describe anxiety, the ego, and the superego. In the title of this book, "stress" implies an almost physical quality, which, in the physical sciences can be measured, weighed, and mathematically studied. By use of such terminology, the authors seem to be striving to give their hypotheses factual qualities. Anxiety is described by such words as "free-flowing," "pressure," "blocking," "waving," and "free-floating." Such qualitative and quantitative expressions are in constant use, both in the clinical descriptions and in the pages which follow each case to interpret and explain the theories.

It should be noted again that the criticism of this book is not intended, primarily, for the psychiatrically trained reader. It is written for those who are interested in finding out something about the war neuroses as a part of a general understanding of the neurotic personality which comes into the general experience of physicians whose interests lie chiefly in the field covered by *Surgery, Gynecology and Obstetrics*. It should be made clear, to the general reader, that the conceptions of the neurotic mechanism, so insistently emphasized, are not to be taken as verifiable, but rather as a working scheme for which the authors have a strong predilection. The reviewer is referring specifically to the dynamic picture of the ego and superego, mention of which is found on almost every page of this book. A critical examination of these Freudian concepts of the personality and of the theories of the neuroses built upon these concepts has no place in this review. As working hypotheses, they have become the permanent possessions of present day psychiatry and their value cannot be overestimated. In this book, however, the two systems and structures of the ego and superego act as beings and not as functions. They are endowed with capacities, qualities, and drives which are often specific and exclusive and leave with the reader the picture of a personality made up of two hostile gangs, forever at odds with one another, forever quarreling for mastery with sly and cunningly devised plots and schemes providing an atmosphere reminiscent of the Kentucky or Tennessee mountain feuds. In this embattled area, the writers find no place for the great instinctive contender—the id. Its omission is strange and it is not explained.

In the chapter on psychodynamics, the central item in the causation or in the strategy of the neuroses is anxiety. About the meaning and implication of this affective state, there have been endless discussions and polemics. The key to the understanding of the neuroses is the understanding of anxiety. This understanding is not facilitated by limiting one's conception of anxiety to apprehension and to loss of some loved one or object; nor by attaching its conscious reactions to the ego. Anxiety has to do with the totality of a human being. Such a fundamental thing, so tied up with the maintenance of the integrity of a being, cannot and should not be limited to only one part of the personality. Nor is it likely that anxiety has its roots in past experience; nor does it necessarily depend on them. Anxiety seems, rather, to be the affective response of a person to situations in which disintegration threatens. The integrity of the organism is at stake. Anxiety stimulates fear or even arouses it and thus the attachment to some specific object or objectives is facilitated. The term, free-flowing anxiety and attached anxiety would seem to be a contradiction. It is a device used frequently by the authors to add a realistic touch to this and other emotional reactions by endowing them with physical qualities, such as flowing, damming up, pressure, and so forth. There is little doubt of the usefulness of such devices, but one can wonder if the gain achieved in clarity is sufficient to neutralize the risk of fixing, in the reader's mind, theoretic ideas of the distorted personality as established facts.

The readers of this book, and there should be a great many of them, will not all have knowledge of the methods of psychiatric interpretation. Lacking it, they may get impressions, perhaps lasting ones, of a mechanical human being with devices for its actions in war and peace, for which no experimental proof has been obtained. It is for this reason that the reviewer has thought it necessary to point out some of the imperfections of the authors' thinking

on these vital questions. The reader will be so interested and entertained by the case reporting and by the general story that he will fail to see anything out of the way with the planned dynamics of the men under stress. There is too much good in this book to warrant quibbling over what, to him, are unimportant matters.

Psychiatry has suffered, in comparison with other branches of medicine, from a tendency to a too ready acceptance of working hypotheses as facts. What appears to be aspects of the truth in personality structure, are, in reality, simply outlines or frameworks to strengthen the explanation and interpretations. This lends a degree of smoothness and tangibility which is deceptive. For example: the clear picture, from this book, of the ego and the superego in a chronic state of "a-fittin' and a-feudin'," is a doubtfully accurate statement of what happens to a personality whose structure has been discordantly shocked by war experiences.

The average reader, and possibly the more technically trained one, will find the chief interest of this book to be in the treatment and handling of the war-neurotic aviators, rather than in the psychological interpretations of the thing that caused his military disability. He will lose interest in the question of anxiety, regression, the ego, and the superego fights, but will be concerned with what is being done for them therapeutically. The chapter on treatment and results is much more brief than its importance would seem to indicate. This, at first sight, seems an error in value judgment. But this is only a superficial view because, in the body of the book which is made up of protocols of individual cases, the authors never lose sight of the treatment and the reasons for the many types of therapeutic efforts. One of the outstanding excellencies is the infiltration of the case reports with the treatment problem. Along with this, there is discussion of the problems based upon the psychological schemata chosen by the authors. This includes the type of therapy used and the reasons for it, in with the basic psychological schemes of the psychodynamics of the situation. As a result of this conception of clinical reporting, the reader, in each case report, has the conviction that a therapy is in the process of being developed. There results a kind of completeness and wholeness, as if the story were told from beginning to end.

The special chapter on treatment, is, therefore, a summing up and the reader is prepared to accept what is written there because he has become pretty well acquainted with it before. This book deals almost exclusively with the aviation wing of the combatant forces and mostly in actual combat environment. Some material is from the convalescent hospital in this country where the authors are, at present, in active service. The clinical material, therefore, includes the pilot, the crew, the ground forces, and the rest of the personnel who comprise the working organization of a flying unit. This focuses the attention of the study on the activities of the members of the crew in combat, photography, reconnaissance, flight formation, and so forth. The aviation wing of the forces is a very selective group from the standpoint of physical fitness, youthfulness, intelligence, and technical training. The screening for aviation is much more meticulous than for the army as a whole. The possibility of physical defects, especially in the special sense organs, is reduced to a minimum. The absence of certain phases of the neuroses among flyers, as contrasted to the infantry, can therefore be well understood. Flyers, as a rule, are better housed, fed, rested, and have better recreational facilities. All this adds up to the fact that they should be more amenable to effective treatment, though they more readily succumb to war traumas.

The mobility of the flying forces, so important a factor in decreasing the number and seriousness of war neuroses in the ground forces, is a constant and not an occasional factor. The stresses are, perhaps, more violent, but their duration is more brief. Group organization is tighter, smaller, and much more essential to the smooth working of a crew than it is in other arms of the services. All this means that, on this material, therapeutic efforts should be more effective than anywhere else in the services, even though there are, necessarily, few statistical confirmations.

No new types of treatment are described, but there are novel and interesting modifications of methods used in the first World War. Narcosynthesis is far better organized and developed than was formerly possible. Hypnosis was used then and is in use now, but is less effective, on the whole, than pentothal sleep. Shock treatment, the most recent addition to the therapeutic measures in psychiatry has a very limited use in the flying forces. The authors are very right in discarding this method and their reasons for so doing are pertinent. They place their main emphasis on narcosynthesis and the somnalent state produced by intravenous pentothal. This represents an advance in procedure of great importance for this drug acts quickly and routinely with few bad aftereffects. Such a drug was not available in World War I, and attempts at producing the same effect had to be made with cruder drugs such as earlier forms of the barbiturates, bromides, and chloral hydrate. Ether and gas were also used for producing this somnalent state.

The use of dream material to obtain descriptions of experiences in an emotional state was regarded then, as now, as a valuable source of information about the individual soldier undergoing treatment. Group therapy, not then called by such a good term, was an automatic necessity owing to the large number of cases and the scarcity of trained psychotherapeutists. There is very little mention of these earlier efforts and no mention at all of the man who, without doubt, is responsible for the beginnings of the important place psychiatry has achieved in this war—Dr. Thomas Salmon.

It should be clear in the readers' minds how narcosynthesis works and what it attempts to accomplish.

It is well to repeat here that the authors regard the use of pentothal, not as a treatment, but as a means of acquiring repressed or forgotten material, which can then be joined to the ego function in an effective synthesis. Consciousness then becomes the final arbiter and can choose the proper and healthy utilization of the traumatic experiences, as experiences. By so enabling the soldier to face himself, the original traumatic situation and its emotional consequences, psychotherapy plus narcosynthesis releases the energy by which he becomes an integrated personality. This is a sound and intelligent therapy and it does not matter much what descriptive terms are given to the mechanisms which are active in the process of synthetic build-up. This rough and skimpy sketch of the therapeutic purposes of narcosynthesis does not begin to consider the techniques that are necessary to accomplish this purpose. Careful psychiatric knowledge and experience are necessary. In this book, they are described with care and minuteness.

The authors give detailed consideration to the limitations of the military psychiatrist and point out, wisely, that his job is primarily a military one and defined by military needs. His main duty and responsibility is to return to active duty as many patients as he can, and to prevent the occurrence of a neurosis in as many combatants as is possible. If the military authorities are convinced of his good faith in these two essentials, his advice on the final disposition of cases is generally followed. In this respect, military psychiatry differs from its peacetime brother in the final therapeutic goal. To change, revise and alter a disruptive environment is an important part of civil psychiatric effort. In war, the psychiatrist cannot possibly affect the arrangement or qualities of combat or precombat areas. He should try to return his cured war neurotic to the traumatic environment that originally produced the neurosis. This war necessity cannot be too greatly stressed and in this book it is amply and emphatically pointed out.

Men Under Stress is a book which will take its place as a permanent contribution to the knowledge already accumulated of the neuroses in this and the first World War. In spite of its length and its hurried, breathless style in places, there is no question of its value and pertinence, especially at the present time. Its appeal rests largely on the very human quality which the authors have put into their writing. It is the story of men under battle and war-borne stress. It is also the story of a small group of men, themselves in the atmosphere of conflict, who give freely and generously of their training, experience, knowledge, and good faith, to help the infinitely larger group of men who have succumbed, temporarily or permanently, to the forces in the stress and stresses of war. It is finally the story of conflict where the enemy is no longer the armed might of opposing armies, but the unarmed might of the neuroses.

Eight years ago, Freud wrote these words, "What is the source of the neuroses? What is the ultimate, its specific, underlying principle? After decades of analytic effort, this problem rises up as untouched as at the beginning." S. J. SCHWAB.

CORRESPONDENCE

SEGMENTAL RESECTION OF LESIONS OCCURRING IN THE LEFT HALF OF THE COLON WITH PRIMARY END-TO-END ASEPTIC ANASTOMOSIS—A Correction

IN the December, 1945, issue of SURGERY, GYNECOLOGY AND OBSTETRICS, volume 81, page 593, in the article entitled "Segmental Resection of Lesions Occurring in the Left Half of the Colon with Primary End-to-End Aseptic Anastomosis; Report Based on Fifty Cases" by John M. Waugh and Monford D. Custer, Jr., the authors erroneously stated that Gibbon and Hodge had reported the mortality after exteriorization operations on the colon as 99 per cent. The figure should have been 29 per cent (14 patients, 4 deaths) as stated in Table II in the article by Drs. Gibbon and Hodge.